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Effects of cardiorespiratory exercise on motor skill learning and cognitive executive functions in Parkinson's disease

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Thèse présentée à la Faculté des arts et des sciences
en vue de l'obtention du grade de doctorat (Ph. D.)
en psychologie -recherche et intervention-
option neuropsychologie clinique

Décembre, 2016

Résumé

La maladie de Parkinson (MP) est la deuxième maladie dégénérative la plus répandue au Canada. Elle se caractérise par des symptômes moteurs importants tels le tremblement de repos, la rigidité musculaire, l'instabilité posturale, la lenteur dans les mouvements ainsi que par des symptômes non moteurs, notamment une diminution du fonctionnement cognitif. Conséquemment, la nature hétérogène des symptômes de la MP dirige bien souvent l'individu atteint vers une sédentarité physique et mentale involontaire.

Les traitements pharmacologiques et neurochirurgicaux demeurent les approches thérapeutiques majoritairement choisies. Toutefois, de plus en plus d'études visant à examiner les impacts de l'exercice physique aérobique (EPA) ont démontré des bénéfices de ce traitement non pharmaceutique, entre autres, en améliorant les symptômes moteurs de la maladie. Néanmoins, l'effet de l'exercice sur la cognition et l'apprentissage moteur à travers la MP est encore méconnu. Ainsi, ce projet de thèse vise à étudier les changements cognitifs et moteurs suite à un entrainement cardiovasculaire. Une première étude visait à mesurer les changements comportementaux au niveau de la capacité aérobique, des fonctions cognitives dites exécutives et de l'apprentissage procédural moteur suite à l'EPA. Une deuxième étude utilisant l'imagerie par résonance magnétique fonctionnelle (IRMf) permettait ensuite d'identifier les corrélats neuronaux associés à l'effet de l'EPA sur l'apprentissage moteur.

20 participants en santé et 19 atteintes de la MP, âgées entre 40-80 ans, ont participé à un programme d'entrainement de 3 mois (3 fois/semaine) à une intensité élevée, débutant à 20 minutes (+5 minutes/semaine) pour atteindre 40 minutes d'EPA. Le niveau d'intensité de

base a été prescrit selon la capacité aérobique initiale du participant en réponse au test à l'effort effectué (pré et post entraînement). Plusieurs mesures d'évaluation physiques (*VO_2peak*, pression artérielle, fréquence cardiaque) et neuropsychologiques (« *Stroop, trail making test » (TMT)*) ont été prises en début et à la fin de l'entraînement. De plus, des sessions d'acquisition de données cérébrales fonctionnelles grâce à l'IRMf ont été administrées durant la passation d'une tâche d'apprentissage moteur implicite (tache : « *Serial Reaction Time Task »(SRT)).*

Les résultats ont montré que l'entraînement en EPA fut efficace car une amélioration significative de la capacité aérobique fut observée chez tous les participants. Au niveau comportemental, l'EPA a eu pour effet d'améliorer les capacités d'inhibition (Stroop) et d'apprentissage moteur (SRT), mais pas celle associée à la flexibilité mentale (TMT). Pour leur part, les données de neuroimagerie ont révélé une augmentation de l'activité fonctionnelle liée à l'amélioration de l'apprentissage moteur au niveau de l'hippocampe, du striatum et du cervelet, et ce en comparaison avec les sujets contrôles. De plus, les changements fonctionnels chez les individus atteints de la MP étaient corrélés au changement de la capacité aérobique : une relation positive fut liée à l'augmentation de l'activité de l'hippocampe et du striatum, tandis qu'une relation négative fut observée au niveau du cervelet.

Ce projet est l'un des premiers à mettre en lumière l'impact clinique d'un traitement non pharmaceutique visant à améliorer la nature motrice et cognitive des symptômes de la MP, ainsi que de proposer les mécanismes neurofonctionnels pouvant expliquer l'amélioration observés au niveau de l'apprentissage suivant l'entrainement en EPA. Ainsi, nous croyons que les résultats de cette étude serviront les milieux cliniques et la population de patients atteints

de la maladie de Parkinson en proposant une solution thérapeutique efficace et économique afin d'améliorer la qualité de vie de ces derniers.

Mots-clés : Maladie de Parkinson, exercice, cognition, moteur, fonctions exécutives, mémoire procédurale, neuroimagerie

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder in Canada. It is mainly characterized by important motor symptoms such as slow movement, tremor, rigidity and problems with locomotion, but non-motor symptoms (NMS) such as cognitive dysfunctions are also present early in the disease. Inadvertently, the heterogeneous nature of PD's symptoms may lead to an unintentional sedentary behaviour both at the physical and mental level.

To date, the most common forms of PD treatments remain pharmacological and neurosurgical in nature. Most recently, however, studies have demonstrated benefits of aerobic exercise training (AET) as a non-pharmaceutical treatment with significant effects on PD's motor symptoms. Nevertheless, the effects of exercise on cognitive and motor learning function in PD remain unknown. Thus, this thesis project aims at studying cognitive and motor changes following AET. Most specifically, the first study intended to assess behavioural changes related to aerobic capacity, cognitive (executive) functions and procedural learning following three months of AET. The second article used functional magnetic resonance imaging (fMRI) to identify the neural correlates associated with the effect of AET on motor learning.

Twenty healthy controls (HC) and 19 early PD individuals, aged 40-80 years old, participated in a supervised high intensity stationary recumbent bike training program (3 times/week; 12 weeks). Exercise prescription started at 20 minutes (+5 minutes/week up to 40 minutes) based on participants' maximal volume of oxygen uptake (pre and post training). Several physical (VO2peak, blood pressure, heart rate) and cognitive (Stroop and Trail making

tests (TMT)) measures were used pre and post AET. Importantly, participants' procedural learning skill (implicit motor learning) was evaluated using a version of the Serial Reaction Time Task (SRT) during the acquisition of functional neuroimaging data.

AET program was effective as indicated by a significant improvement in aerobic capacity in all participants. At the behavioural level, AET improved inhibition (Stroop) and motor learning (SRT), but not flexibility (TMT). Brain imaging data revealed pre-post MSL-related increases in functional activity in the hippocampus, striatum and cerebellum in PD patients as compared to controls. Importantly, functional brain changes in PD individuals correlated with changes in aerobic capacity: a positive relationship was found with increased activity in the hippocampus and striatum, while a negative relationship was observed with the cerebellar activity.

This project is one of the first to elucidate the clinical impact of such non-pharmaceutical treatment targeting motor and non-motor aspects of PD. Accordingly, it is believed that the results will be of use for clinical settings and for the population of patients with PD, as they give evidence in favour of an efficient and economical therapeutic solution for PD.

Keywords : Parkinson's disease, aerobic exercise, cognition, motor, executive functions, procedural learning, neuroimaging

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List of Abbreviation

AET: Aerobic exercise training

BDNF: Brain derived neurotropic factors

CC: Cortico-cerebellar

CS: Cortico-striatal

DBS: Deep brain stimulation

EPA: Exercice physique aérobique

FITT: Frequency, intensity, time and type

fMRI: Functional magnetic resonance imaging

HC: Healthy controls

IRMf: Imagerie par résonance magnétique fonctionnelle

MCI: Mild cognitive impairment

MP: Maladie de Parkinson

MSL: Motor sequence learning

NMS: Non-motor symptoms

PD: Parkinson's disease

QOL: Quality of life

RT: Reaction time

SRT: Serial Reaction Time

STN: Subthalamic nucleus

TMT: Trail making test

UPDRS: Unified Parkinson's disease rating scale

VO2max: Maximal volume of oxygen uptake

À toi, mon cher JB, qui a si bien su m'accompagner à travers les 1001 aventures de l'univers du doctorat

Remerciements

Julien, merci de m'avoir fait confiance dans la mise en place d'un nouveau, beau et gros projet de recherche dans le labo. Ce défi m'a fait traverser toutes les gammes d'émotions, mais celle qui ressort davantage est la fierté.

Freja et Gen, à des moments clefs de mon parcours, vous m'avez partagé sans limites vos compétences et passions pour la recherche. Vous êtes des femmes extraordinaires, je vous remercie énormément.

Francine, Arnaud et Ovidiu, vous apportez au labo des ressources incommensurables et complémentaires. Merci de votre compétence et très grande générosité au cours de mon cheminement.

Catherine, je me souviens de t'avoir raconté ma première journée à la maternelle et de mon amie Catherine. Cette association naïve m'avait permis d'apaiser mes peurs et mes angoisses dans mes débuts de scolarisation. Je constate que mon amitié avec toi tout au long du cheminement doctoral m'a permis de nommer ses grandes émotions que nous fait vivre le monde en parallèle du doctorat en R-I. Je te remercie pour ta personnalité si attachante et colorée ainsi que ton écoute et ta présence si importantes durant mon cheminement. Ta compréhension et ton soutien à plusieurs niveaux ont rendu mon expérience doctorale humaine et je t'en suis fort reconnaissante.

Maman et papa, votre soutien et amour inconditionnel sont la base essentielle d'un si grand accomplissement. Cet amour a permis de faire fleurir mon autonomie, une capacité indispensable pour l'obtention du doctorat. Merci.

JB, la personne que l'on côtoie le plus souvent est malheureusement celle qu'on oublie de remercier à sa juste valeur. J'ai tant de reconnaissance pour toi. Tu as été le premier à m'encourager à m'inscrire au doctorat et jamais depuis tu n'as douté une seule fois de ma réussite. Tu as su t'adapter aux circonstances difficiles et m'offrir tous les besoins nécessaires pour vivre cette expérience harmonieusement. Merci du fond du cœur, je t'aime.

Chapter I: Theoretical Background

1. Introduction

1.1. Parkinson's Disease Etiology

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It affects approximately 1% of the population over the age of 55 years and has a mean age onset of about 60 years (Hayes, Fung, Kimber et O'Sullivan, 2010). In Canada alone, PD is affecting more than 100,000 Canadians today, and unfortunately, current demographic trends predict that the number of cases will double by 2050 due to the expected increase in the size of our elderly population. As such, the development of knowledge and the implementation of new therapies to treat PD remain a major objective for our society. The primary treatment approaches of this disease remain pharmacological (e.g., L-Dopa and others) and neurosurgical in nature (e.g., deep brain stimulation). Yet, as these methods come with obvious risks and limitations due to adverse side effects, research dedicated to finding alternative means to alleviate the symptoms, and possibly to slow down the pathophysiological process of the disease, is of paramount importance. One of those treatments, which has gained empirical and clinical attention over recent years, is aerobic exercise training (AET). The present thesis aimed to investigate further the clinical benefits of such an alternate individualized therapeutic approach for patients with early PD.

1.2. Motor and Non-Motor Dysfunctions

The most common form of Parkinsonism is called idiopathic (with unknown cause). PD is defined by a multidimensional spectrum of symptoms, involving the classical motor

symptoms (slow movement, tremor, rigidity and problems with locomotion) and non-motor symptoms (NMS), such as autonomic, sensory, sleep and neuropsychiatric dysfunctions. Although those symptoms are observed in patients, they are known to vary greatly, especially at the beginning of the disease process. Yet, different characteristics of PD have been identified, for instance, based on an early versus late onset of the disease, rapid versus slow disease progression, akinetic-rigidity versus tremor predominant (TD) or postural instability/gait difficulty (PIGD) vs tremor predominant (Chen et al., 2015; Lewis et al., 2011; Marras, 2015; Thenganatt et Jankovic, 2014). Most recently, subtyping has emerged in the literature to understand better the heterogeneous nature of PD. To date, motor subtyping has dominated the landscape of research (Marras et Chaudhuri, 2016), but mounting evidence for the relevance of non-motor features in PD subtypes (e.g. cognitive impairment, orthostatic hypotension, and rapid eye movement sleep behavior disorder—RBD) is rising (Fereshtehnejad et al., 2015). As such, PD is now defined by a multidimensional spectrum of motor and NMS reflecting a rather complex and heterogeneous nature of the disease's process.

Certainly, the striatal dysfunction in PD is known to be responsible for the chronic, heterogeneous and progressive nature of this movement disorder. Specifically, PD is characterized by a significant loss of dopaminergic (DA) neurons in the basal ganglia, and more specifically in the substantia nigra *pars compacta* that projects to the striatum through the nigro-striatal pathway. Functionally, the dopaminergic system innervates the basal ganglia structures, hence facilitating movement control and organizing networks for associative motor learning and planning (Obeso et al., 2008). Structurally, the motor circuit of the basal ganglia

implicates predominantly the striatum (the putamen in particular), the subthalamic nucleus (STN), the globus pallidus pars interna (GPi) and externa (GPe), as well as the substantia nigra pars reticula (SNr), these structures communicating with cortex through the thalamus. Then, from a neuropathological point of view, the motor deficits in PD have been found to be due to an increased in neuronal activity in the STN and GPi/SNr, causing a cortico-striatal imbalance, which leads to excessive inhibition of thalamocortical and brainstem motor nuclei. Moreover, it is estimated that approximately 80% of striatal DA neurons have declined before classical motor symptoms of bradykinesia, rigidity and resting tremors appear (Stoessl, 2011).

Accordingly, before significant neuropathological (DA) degeneration manifests itself at the motor level, a pre-motor phase of the disease is characterised by NMS (Goldman et Postuma, 2014; Lee et Koh, 2015; Obeso et al., 2008; Rana, Ahmed, Chaudry et Vasan, 2015). The NMS of the disease are critical determinants of health-related quality of life and can antedate clinical motor manifestations in PD by years and even decades (Rana et al., 2015). This latter includes autonomic dysfunctions (e.g. orthostatic hypotension, constipation, urogenital dysfunction), sensory symptoms (e.g. olfactory dysfunction, abnormal sensations and pain), sleep disorders (e.g. insomnia, REM behaviour disorder, restless leg syndrome, excessive daytime somnolence) and neuropsychiatric dysfunctions (e.g. mood disorders, frontal executive dysfunction) (Poewe, 2008; Rana et al., 2015). Psychiatric NMS (e.g. hallucination, impulse control disorders) are also known as an outcome of dopamine replacement therapy (PD most common treatment) and may also occur at all stages of PD, more specifically when levodopa treatment has modified the striatal serotonin level within the brain (Lee et Koh, 2015).

Hence, PD is now recognized as a multi-system disorder with motor and non-motor features. The clinical nature of NMS reflects the widespread neurochemical and neuroanatomical changes that occur throughout the course of PD, involving not only the dopaminergic nigrostriatal system (as mentioned above), but the serotonergic and noradrenergic brainstem areas as well as the cholinergic frontal and brainstem regions (Goldman et Postuma, 2014). In fact, Braak and colleagues (2003) have suggested that the earliest pathological evidence of PD is found in the gastrointestinal system as well as the medulla and olfactory bulb, before years of anatomical manifestations (in the substancia nigra *pars compacta* and the cortex) converge with both motor and non-motor expressions.

To date, the clinical course of NMS in PD is of growing interest, but the literature is still in its infancy when compared to the plethora of studies on motor symptoms. Yet, we know that non-motor features of PD are common, associated with poor outcomes, and implicate several non-dopaminergic systems (Goldman et Postuma, 2014). However, we also know that improved therapeutics to treat NMS are awaiting. For instance, neuropsychiatric disorders, such as depression and anxiety are two of the most common NMS observed in *de novo* PD patients compared with the general population (de la Riva, Smith, Xie et Weintraub, 2014). Although de la Riva et al. (2014) found that early neuropsychiatric symptoms are stable (in severity) over the first two years of the disease, these NMS may have a deteriorating and devastating impact on quality of life and cognitive functions over the course of the disease. In fact, a systematic review on cognitive and neuroanatomical correlates of neuropsychiatric symptoms in PD revealed that executive dysfunctions are common in patients with depression at the moderate to severe stages of PD (Alzahrani et Venneri, 2015). Nevertheless, since

cognitive dysfunction is also a NMS, the apparent difficulty in determining whether the mood disorder precedes cognitive decline, or vice versa, remains of interest to future research. More specifically, the development of knowledge on underlying neurobiological mechanisms of NMS in PD may provide such understanding.

Besides, literature reviews on the cerebellum and PD provides further understanding on the motor and NMS of the disease. In fact, studies have shown that the cerebellum is not only involved in the pathophysiology of PD *per se*, but also in compensatory mechanisms (Lewis et al., 2013; Wu et Hallett, 2013). On the one hand, as the dopaminergic degeneration developed within the striatum, the hyperactivity of the cerebellum seems to contribute to several clinical symptoms (e.g. tremors) (Chen et al., 2015; Martinu et Monchi, 2013). On the other hand, studies suggest that the cortico-cerebellar (CC) system is also capable of compensating when the cortico-striatal (CS) pathway is functionally impaired, for example, during motor execution and motor learning processes (Bédard et Sanes, 2009; Doyon, 2008; Lewis et al., 2013; Sen, Kawaguchi, Truong, Lewis et Huang, 2010; Wu et Hallett, 2013). For instance, in a well-designed series of studies using a trial-and-error, reaching sequence learning paradigm as well as image subtraction and network-based statistical analyses of PET data, Eidelberg and colleagues (Carbon et Eidelberg, 2006; Eckert et Eidelberg, 2005; Eckert, Tang et Eidelberg, 2007) have shown that patients with Parkinson's disease demonstrate abnormal task-related patterns of activations within the CS system compared with matched control participants. In fact, evidence indicates that they rely more on the CC system, as reported by Mentis et al. (2003) suggesting that PD patients need to activate a greater volume of the cerebellum to achieve equal performance levels on this trial-and-error reaching

sequence task; the latter findings being consistent with Doyon's model (2005b) of the neural changes associated with motor learning. Altogether, these results suggest that the CC system is capable of compensating when the CS pathway is functionally impaired. Furthermore, as both the CS and the CC circuit systems influence cerebral cortical activity via independent and interconnected links (Bostan et Strick, 2010a), compensatory mechanisms in the cerebellum could be involved in motor as well as cognitive and affective functional roles of the cerebellum.

2. Literature Review

2.1. Motor Skill Learning

Motor skill learning constitutes a type of procedural learning where new movements, either produced alone or in a sequence, come to be performed effortlessly through repeated practice. It is characterized by different learning processes (fast, slow, automatization), and the learning is known to be incremental, long-lasting and dependent upon anatomical and functional plasticity in motor-related brain structures, including the CS and CC systems (Doyon et al., 2009; Doyon et Benali, 2005a) as well as the cervical spinal cord (Vahdat et al., 2015). To study this phenomenon, researchers have most often used motor sequence learning (MSL) tasks designed to measure one's ability to integrate simple stereotyped finger movement into a single motor representation. Learning of this type of ability can be explicit (i.e., the subject knows the sequence of movements to perform before practicing it until it becomes automatic) or entirely implicit in nature (i.e., without knowing that a sequence is embedded in the series of movements that the subject is performing). The latter is a process where knowledge is acquired simply through exposure, and will be the focus in this research project.

In this project, we investigated implicit motor learning, a process involved in many of our daily motor skills (e.g. typing). Quite often we learn specific sequential regularities through repeated practice, without necessarily intending to do so or without being able to articulate what exactly has been learned, hence suggesting that motor sequence skills can be acquired in an unconscious way (Destrebecqz, 2001; Stadler, 1998). Within the field of implicit motor sequence learning, the Serial Reaction Time (SRT) task originally developed by Nissen et Bullemer (1987b) has been by far the paradigm most extensively used to measure this type of memory. In the SRT task, a visual stimulus appears at one of the four horizontally aligned positions on a computer screen. Participants have to react as fast and as accurately as possible to the location of the stimulus by pressing the spatially corresponding key. Without their knowing, the succession of stimuli (and hence responses) follows a repeating sequence. With continued practice, reaction times (RTs) become much faster on trials following the sequence than on trials violating the sequence (i.e., that are presented at random). These RT differences between sequenced and non-sequenced (random) trials indicate that participants have learned the sequence. The SRT task is thus an optimal experimental paradigm to study implicit sequence learning given the relative simple experimental implementation, the facts that sequences are typically acquired rapidly and because it is an objective way to assess sequence learning (Clegg, DiGirolamo et Keele, 1998). This is also particularly true when one wishes to study subjects' ability to learn a new motor sequence at several time points (e.g. before and after a program of aerobic exercise).

From a neuro-functional system viewpoint, the verdict with regards to the implicit learning capacity in PD is still inconclusive, especially as it relates to SRT literature. For instance,

a meta-analysis of SRT studies in PD patients concluded that implicit sequence learning is impaired in PD relative to healthy controls (Siegert, Taylor, Weatherall et Abernethy, 2006), while other studies concluded that implicit learning is preserved in the initial phase and progressively deteriorates over the course of the disease (Abbruzzese, 2009; Muslimović, Post, Speelman et Schmand, 2007). The most recent meta-analysis and meta-regression on SRT task performance, which analyzed 27 studies, concluded that worse sequence learning was observed in PD than in control matching group (Clark, 2014). Yet, PD implicit MSL literature is not unequivocal, as a set of studies has pointed out that task complexity, learning stage, disease severity, dopaminergic medication and sequence awareness as exacerbating factors that may interfere on learning capacity (Gamble et al., 2014; Ruitenberg, Duthoo, Santens, Notebaert, & Abrahamse, 2015). For instance, Gamble et al. (2014) conducted a study in patients with PD and healthy older adults who completed three sessions (10 blocks of 50 trials) of an implicit sequence learning task. Their analyses were based on a processing based model, which suggests that the hippocampus is involved in repeated encoding and reconsolidation (1st half of the block design), and may disengage as the striatal functions of the proceduralization process (2nd half of the block design) take over (Henke, 2010). Results demonstrated that both groups were capable of learning. When they compared first vs. second half of motor learning trials, however, a significant difference between groups was observed. While the control group showed learning throughout the task, the PD group showed learning only in first semi-portion of the task. They concluded that early PD's patients had an intact hippocampal-dependent implicit sequence learning, but an impaired striatal dependent learning capacity (Gamble et al., 2014).

The latter findings are consistent with Doyon's model of brain plasticity associated with MSL (Albouy et al., 2015; Doyon, Penhune, & Ungerleider, 2003 Doyon et al., 2009), as it proposes that in the fast learning phase, MSL recruits the striatum and the hippocampus, as well as the cerebellum, motor cortical regions, and prefrontal and parietal cortex. During this stage, dynamic functional interactions between these structures are thought to be critical for establishing the motor routine necessary to learn the new motor skill. Converging evidence from human neuroscience research carried out in Doyon's laboratory and others has also stressed the role of the CS circuit during implicit MSL (see Doyon, 2008; Doyon et al., 2009; Doyon & Benali, 2005; Doyon et al., 2011; Doyon et al., 2003; Doyon & Ungerleider, 2002, for reviews). For example, numerous imaging studies using fMRI or positron emission tomography (PET) techniques found increased activation in the striatum during implicit SRT learning (Destrebecqz et al., 2005; Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Peigneux et al., 2000; Rauch et al., 1997). 11C-Raclopride PET experiments have also shown significant endogenous dopamine release in the caudate and putamen during early stages of implicit SRT learning in young (Badgaiyan, Fischman, & Alpert, 2007) and older subjects (Garraux, Peigneux, Carson, & Hallett, 2007). Most recently, fMRI studies showed respective roles of the hippocampal and the striatal structures in MSL, suggesting that such complex learning memory process requires the recruitment of both systems as a function of spatial memory and motor task, respectively (Albouy et al., 2015; Albouy, King, Maquet, & Doyon, 2013).

Yet to our knowledge, evidence related to the brain structures involved during MSL in PD is limited in the literature. In fact, there have been only two studies that investigated brain activation patterns between PD and healthy controls (HC) during implicit SRT learning

(Schendan, Tinaz, Maher, & Stern, 2013; Werheid, Zysset, Müller, Reuter, & von Cramon, 2003). In Werheid et al. (2003) study, results suggested that rule learning (seq >rand) was possible in both groups and that this correlated with highly similar fronto-median and posterior cingulate activation for both groups, although striatal activation was only present in HC subjects. Their study, however, was limited by the facts that only seven subjects were included in each group, most subjects reported awareness of the sequence, the early phase of sequence learning was not scanned, shorter duration of random blocks compared to sequence was used, and the fMRI acquisition excluded the cerebellum; an important structure of the motor system involved in motor sequence learning as well. In Schendan et al. (2013), the study aimed at comparing functional brain response patterns in the medial temporal lobe (MTL) and basal ganglia (regions of interests; ROIs) during the early acquisition phase of an implicit sequence learning task (Schendan, Searl, Melrose, & Stern, 2003) in three groups of participants: PD patients, healthy matched elderly controls and younger control participants. The results showed that the sequence-specific learning (seq > rand) of higher-order associations were reduced with age, and changed even further in the PD group, as revealed by reduced intensity and extent of sequence learning-related activation in fronto-striatal and MTL circuits. For the PD group only, the sequence-specific learning (reaction time) varied across trials, which corresponded to an over-recruitment of brain regions (ROI's) throughout the SRT task in both conditions (random and sequence). In addition, PD showed changes in MTL beyond the changes in normal aging: right MTL hypoactivation (exacerbation of aging pattern) and left MTL hyperactivation. They concluded that PD affects sequence learning and memory functions, as the MTL and striatal brain changes were differently involved compared to normal

aging brain processes. Unfortunately, the cerebellum was not included in the analysis, and thus no conclusion can be drawn on whether or not such important motor brain structure was involved during the learning process. In sum, in PD patients, regions similar to those observed with aging seem to be recruited during MSL functioning, but altered brain mechanisms of the CS and MTL are observed. Moreover, to develop a complete understanding of such functional process in PD, studies should include the cerebellum while investigating motor tasks, as it has been linked to motor skill learning functions. Overall, it thus seems that PD patients are typically capable of learning a new motor sequence, but that their learning ability is impaired and less efficient than matched healthy older subjects.

2.2. Cognition

It is now well documented that a phase of mild cognitive impairment (MCI) may precede the motor deficits in PD (Aarsland, Brønnick et Fladby, 2011; Beyer, Janvin, Larsen et Aarsland, 2007; Braak, Rüb et Del Tredici, 2006; Ibarretxe-Bilbao, Tolosa, Junque et Marti, 2009; Lin et Wu, 2015; Monchi, Hanganu et Bellec, 2016). For example, Aarsland and colleagues (2011) have conducted a multicenter pooled data analysis to determine the frequency and profile of MCI in PD, which was defined by one or more cognitive domains (verbal memory, visuospatial, and attentional/executive) that were at least 1.5 standard deviations below the mean of normative data (Aarsland et al., 2011). A total of 25.8 % of PD patients were classified as having MCI, and among those, MCI was mainly found in male gender, and was associated with depression, and severe motor symptoms.

A recent study conducted by Weintraub et al. (2015) examined the prevalence and correlates of cognitive impairment and neuropsychiatric symptoms in early PD compared to

healthy controls. While 22% of PD individuals were cognitively impaired according to the Montreal Cognitive Assessment (MoCA) cut-off, only 9% met detailed neuropsychological testing criteria for MCI. In addition, the PD patients were more depressed and experienced more anxiety than healthy controls. Yet, no association was found between cognitive and neuropsychiatric symptoms. As such, these results highlight that at an early stage of PD, cognitive and neuropsychiatric dysfunctions may coexist silently. However, at moderate to severe stages of PD, a systematic review on cognitive and neuroanatomical correlates of neuropsychiatric symptoms revealed that cognitive dysfunctions in patients with depression are substantial (Alzahrani et Venneri, 2015). Such findings thus suggest that to reduce risk of developing a more severe state of cognitive decline such as PD dementia, signs of cognitive decline are important to detect at an early phase of the disease.

Yet, executive dysfunctions have most often been reported in studies investigating cognition in PD, and again, the symptoms have been found to manifest themselves as an early feature of the disease (Cools, Barker, Sahakian et Robbins, 2001; Elgh et al., 2009; Monchi et al., 2016; Monchi et al., 2004; Muslimovic, Post, Speelman, De Haan et Schmand, 2009; Muslimović et al., 2007; Obeso et al., 2011). PD patients have been found to exhibit problems in tasks requiring inhibition, as reflected by a delay observed in the Stroop interfering effect (Obeso et al., 2011), as well as difficulties in performing cognitive flexibility tasks, such as the Wisconsin card sorting task (Monchi, Petrides, Mejia-Constain et Strafella, 2007). For example, Monchi et al. (2007) conducted an fMRI study and they found that early PD patients have less activation in fronto-striatal than normal controls while executing a behavioural shifting task. Such finding is consistent with a plethora of studies that have reported executive dysfunctions

in this clinical population (see (Antonelli, Ray et Strafella, 2010; Christopher et Strafella, 2013; Hirano, Shinotoh et Eidelberg, 2012; Lin et Wu, 2015; Monchi et al., 2016) for reviews).

Although the executive functions seem to be the predominant cognitive domains affected in PD, the pattern of cognitive dysfunction in this disease is complex and heterogeneous, as some patients also exhibit impairments in memory, language, or visual-spatial functions (Janvin, Larsen, Aarsland et Hugdahl, 2006; Janvin, Larsen, Salmon, et al., 2006; Verreyt, Nys, Santens et Vingerhoets, 2011; Watson et Leverenz, 2010). Although conjectural, such heterogeneity has been thought to be due to the variability in the neuropathological substrates involved. For instance, it is common that at disease onset, patients with PD report that only one side of the body is affected (Djaldetti, Ziv et Melamed, 2006; Toth, Rajput et Rajput, 2004), the latter condition being associated with an asymmetric dopaminergic degeneration in the brain (Eidelberg et al., 1990). Indeed, Verreyt et al. (2011) have shown that patients with right-sided motor-symptoms predominance exhibit problems with language-related tasks and verbal memory, whereas patients with left-sided motor symptoms perform worse on tasks of spatial attention, visuospatial orienting and memory. Moreover, a recent literature review on cognitive dysfunction in PD conducted by Barker et Williams-Gray (2014) highlighted two different cognitive syndromes observed in early PD patients resulting from different aetiologies. One syndrome describes the “Frontal executive impairments” with fronto-striatal malfunctioning and dopaminergic deficits (both in the frontal lobes and the striatum). The other syndrome defines the “Posterior cortical impairments” with posterior cortical Lewy bodies and non-dopaminergic deficits. Although

these profiles of cognitive decline are still debatable, it provides some reflections on possible pathophysiology associated with cognitive decline observed in PD.

In sum, cognitive impairment is one of the most common and devastating non-motor symptoms of this disease and studies agree to say that the cognitive decline varies greatly, suggesting a heterogeneous pathophysiology in PD. Yet, limited amount of studies have investigated the effects of non-pharmacological interventions, and of chronic aerobic exercise in particular as a treatment to improve cognition in this patient population. Considering that aerobic exercise has demonstrated improvement in cognitive abilities (e.g. enhanced executive functions) in healthy elderly individuals ((Predovan, Fraser, Renaud et Bherer, 2012) see), and several other reviews on this ((Audiffren, André et Albinet, 2011; Bherer, Erickson et Liu-Ambrose, 2013b; Colcombe et Kramer, 2003; Voss, Nagamatsu, Liu-Ambrose et Kramer, 2011) for reviews), it seems natural to investigate the effects of such a treatment approach on cognitive functioning in PD. The next section will review the theoretical background for PD treatment with an emphasis on physical exercise, and will develop further on its benefits and effects on the brain.

2.3. Treatment

Dopaminergic-derived treatments have been used for many decades to stop symptoms of basal ganglia dysfunction; the most common approach involving drugs (e.g. levodopa, dopamine agonists, and monoamine oxidase [MAO-B] inhibitors). Although dopaminergic drugs are effective to overcome motor symptoms by reducing striatal neuronal output activity, antiparkinsonian medication is also causing side effects (e.g. dizziness, dyskinesia, involuntary body movement, dry mouth); and may even hinder other NMS, such as cognitive processes

(Ruitenberg, Duthoo, Santens, Notebaert et Abrahamse, 2015). As a result, strict regimen of drug intake regulates patient's daily living.

When drug measures fail, subthalamic nucleus deep brain stimulation (STN DBS) is another effective treatment for PD. In fact, motor function and quality of life (QOL) can be improved substantially in some patients with PD by STN DBS treatment. Yet, it has been reported that on some occasions, patients can develop cognitive and emotional difficulties after surgery (Smeding, Speelman, Huizenga, Schuurman et Schmand, 2011; Troster, 2011). For instance, Smeding and colleagues conducted a study assessing neuropsychological status and quality of life before and post DBS treatment; a year after surgery a profile of cognitive decline was found. Despite motor and quality of life gains, declines in verbal fluency, verbal memory, visuospatial reasoning, attention and processing speed were reported. As such, DBS provides important functional benefits, but at the cost of possible cognitive deteriorations.

Apart from drug and DBS interventions, alternative treatments, such as physical activity, have recently been investigated in PD. Such a new approach is based on an increasing number of studies in animals and humans, which indicate that physical exercise may attenuate symptoms of the disease, and even exert a neuroprotective effect (Hirsch et Farley, 2009b; Hirsch, Iyer et Sanjak, 2016). In animals, for example, mice with PD model forced to exercise on treadmill did not develop behavioural deficits and significantly preserved nigrostriatal neuronal connections as well as striatal dopamine levels compared to sedentary mice (Pothakos, Kurz et Lau, 2009; Shin, Jeong, An, Lee et Sung, 2016; Yoon et al., 2007). Most recently, findings also suggest that exercise may provide beneficial effects to PD's patients by facilitating synaptic plasticity and increasing dendritic spines (Shin et al., 2016). Although the

exact mechanism of action remains unknown, Petzinger et al., (2007) have found that a similar intervention does not change the animals' dopamine levels, nor the amount of neurons in the animals' brains, but improves efficiency of brain dopamine cells more in mice that exercise compared to those that did not. These results suggest that exercise improves neurotransmission efficiency by modifying the areas of the brain (e.g., the substantia nigra and basal ganglia) where dopamine signals are received (Petzinger et al., 2007). As movement is modulated through dopamine, these findings also suggest an interaction between behaviour and cerebral neuronal viability in the striatum after cardiovascular exercise.

In PD patients, studies have demonstrated positive effects of aerobic exercise on functional capacities, such as gait or dexterity (Herman, Giladi, Gruendlinger et Hausdorff, 2007; Monteiro et al., 2016; Ridgel, Vitek et Alberts, 2009; Uhrbrand, Stenager, Pedersen et Dalgas, 2015; van Eijkeren et al., 2008). For instance, Ridgel et al. (2009) conducted a study where ten PD patients were randomly assigned to either a control group involved in voluntary-exercise (VE) (instructed to pedal at preferred rates), or a forced-exercise bicycle program of high intensity (30% of VE rates) for the duration of two months, three times a week. Measures of the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores and functional bimanual dexterity were taken pre-exercise, immediately post-exercise and four months after the end of the program. The results showed that clinical measure of rigidity and bradykinesia as well as biomechanical measures of dexterity were significantly improved in the FE group compared to the VE group, but four months later the pattern of results was then similar between groups. The authors concluded that overall, to gain benefits across disease's symptoms, the high intensity and the chronicity of aerobic training were important.

2.4. Aerobic Exercise Training

Physical activity training can be administered in various ways. On one hand, some studies (Alberts et al., 2016; Coles et Tomporowski, 2008; Dietrich et Audiffren, 2011; Hillman, Kamijo et Scudder, 2011; Hillman et al., 2009; Hillman, Snook et Jerome, 2003; Roig, Skriver, Lundbye-Jensen, Kiens et Nielsen, 2012; Snow et al., 2016) have been interested in the effects of acute training, which corresponds to the short-term effect of one single session of exercise limited in time (e.g. 20 minutes of treadmill exercise). The results have shown that acute effects of exercise on the brain are transitory and that they modify the subject's behavioural and neuronal activity for a certain period of time (Dietrich et Audiffren, 2011). For instance, Roig et al. (2012) have shown that an acute bout of cardiovascular exercise can improve long-term retention of a novel motor skill and that the subjects' capacity to learn seems to be modulated by the intensity of acute aerobic exercise (Snow et al., 2016). On the other hand, chronic exercise, which corresponds to a long-term training period (e.g. three months of bicycle training), has been shown to induce long-lasting effects by modifying the subject's behavioural activity and by inducing brain plasticity. For instance, improved cognitive efficiency of brain structures (e.g. increased density of gray matter and volume of the hippocampus) and functions (e.g. executive functions, memory) have been observed in older adult following chronic aerobic exercise training (AET) (Bherer et al., 2013b).

AET is defined as a structured and repetitive form of exercise with the goal of improving or maintaining physical fitness (Bherer et al., 2013b; Dishman, 2006). In the aging brain, a plethora of studies has observed plastic brain changes following AET ((Bherer et al., 2013b; Erickson, Leckie et Weinstein, 2014; Gregory, Gill et Petrella, 2013) for reviews). In recent

years, there has also been a growing interest in exploring the impact of adding AET to the patient regular treatment regimen, most specifically in PD (Fisher et al., 2008; Herman, Giladi et Hausdorff, 2009; Hirsch et al., 2016; Monteiro et al., 2016). Such studies have explored the role of AET at the behavioural level (e.g. functional aspects) and overall, these reports have revealed that AET ameliorates functional capacity and quality of life (QoL) in PD's patients (Uhrbrand et al., 2015). However, little is known about the functional and structural substrates associated with the therapeutic benefits of AET on performance in motor and cognitive functions. One of the first human studies identifying possible brain mechanisms following AET in PD was conducted by Fisher et al. (2008), who carried out a two-month study where they divided PD patients in three groups to compare the effects of cardiorespiratory intensity exercise levels on PD motor symptoms, functional capacities and neuronal activity using transcranial magnetic stimulation (TMS). People in the high-intensity group exercised three times a week, an hour each time, on a body-weight supported (with harness) treadmill. The second group did low-intensity balance and stretching exercises, while the third group did no organized exercise at all. Over the course of 24 sessions, those in the high-intensity group walked and ran faster than those in the other groups, working up to speeds of five to eight miles an hour (Fisher et al., 2008). They also took longer strides, and had better posture and bigger arm swings, hence indicating that both walking and balance capacities had improved. In addition to functional capacity improvement, corticomotor excitability measured by cortical silent period (CSP) duration in response to a single-pulse TMS was normalized. They concluded that alteration in both dopaminergic and glutamatergic neurotransmission, induced by activity-dependent (exercise at elevated intensity), normalizes basal ganglia hyper excitability.

While exercise has been a beneficial rehabilitative treatment for motor and cognitive functions in various clinical populations (Bertram, Brixius et Brinkmann, 2016; Hasan, Rancourt, Austin et Ploughman, 2016; Kaltsatou et al., 2015; Liu-Ambrose, Eng, et al., 2010; Motl et Sandroff, 2015; Pedersen et Saltin, 2015; Quaney et al., 2009; Volkers et Scherder, 2011), and elderly individuals (Bherer, 2015; Colcombe et al., 2006; Duzel, van Praag et Sendtner, 2016; Gregory et al., 2013; Huang, Fang, Li et Chen, 2016; Kirk-Sanchez et McGough, 2014; Langlois et al., 2012) little is known in regards to the effect of physical activity in PD as it relates to cognition and motor learning. An extensive review of the literature on the effect of exercise in the elderly population and other clinical populations was conducted to implement our study. The next parts will discuss the underlying brain mechanisms and the benefits of such therapeutic effects already observed in older adults. The literature related to the brain, physical exercise and PD will then be presented.

A significant amount of epidemiological, cross-sectional and interventional studies suggests that physical activity has a prophylactic effect (Duzel et al., 2016; Paillard, Rolland et de Souto Barreto, 2015; Vogel et al., 2009). There is increasing evidence that physical activity executed on a regular basis at moderate intensity will decrease risks to sustain certain diseases such as diabetes, obesity, cancer (e.g. breast cancer), osteoporosis, and cardiovascular disease. In the last two decades, studies have shown interest in understanding such effect, specifically on the aging brain. One of the first epidemiological Canadian study (Canadian Study of Health Aging: 1991-1992 and 1996-1997) conducted on 4615 subjects aged 65 years or older identified regular exercise as a protective factor against Alzheimer's disease (Lindsay et al., 2002). They estimated that a physically active senior had 31% lower risk to develop such

neurodegenerative disease. In the same line, other pioneer studies have reported that: 1) dementia is less present in seniors who are physically active at least three times a week or more (Larson et al., 2006), 2) non-active older adults are showing more significant cognitive decline compared to people who are regularly active on a daily basis (van Gelder et al., 2004), and 3) risks of cognitive decline are higher for seniors practising less than an hour of exercise every day (Schuit, Feskens, Launer et Kromhout, 2001). Such findings have contributed to the development of knowledge on the benefits of chronic exercise on cognition. Most recently, a literature review by Bauman, Merom, Bull, Buchner et Fiatarone Singh (2016) updated the epidemiological evidence for physical activity in aging as it relates to reduce cardio-metabolic risk, reduced risks of falls, grown evidence on improved cognitive function and functional capacity, and reduced risk of depression, anxiety, and dementia. The range of benefits of physical activity in aging in regards to chronic disease prevention and risk reduction includes reducing all-cause mortality risk, preventing cardiovascular disease and diabetes, as well as evidence of benefits on lipid levels, hypertension and reducing the risks of cancer (e.g. breast and colon). Moreover, immediate outcomes on psychological (e.g. reduce anxiety and depression, increase well-being) and functional status (e.g. muscle strength and bone density maintenance, activity of daily living and cognitive function improvement) have been reported (Bauman et al., 2016). In sum, physically active seniors are less inclined than sedentary older adults to develop the normal physiological effects of aging, such as cognitive weakening, as exercise seems to exert a protective effect on the aging brain.

While epidemiological studies have reported a positive influence of physical activity on the brain, cross-sectional investigations have helped to identify the relationship between

physical activity (e.g. fitness level) and other outcome variables (e.g. cognition). For instance, Colcombe et al. 2004 was one of the first to conduct an fMRI study to explore the relationship between older adults' cardiovascular fitness (estimated measure of maximal oxygen uptake, VO_2max) and cognitive functions, measured by the flanker test. Following fitness assessment, participants (N=41) were divided into a low-fit or high-fit group; then, both groups were asked to complete the cognitive task while being scanned. The results demonstrated that the high-fit group showed greater task-related activity than the low-fit group in regions of the prefrontal and parietal cortices; regions that are involved in spatial selection and inhibitory functioning. These results thus demonstrate that high fitness levels act on the brain, hence promoting cognitive efficiency. To date, a substantial amount of studies have also investigated the relationship(s) between cardiovascular fitness and brain structures or functions (Erickson et al., 2014; Gordon et al., 2008; Kleemeyer et al., 2016; Maass et al., 2016; McAuley, Szabo, Mailey, Erickson, Voss, White, Wójcicki, et al., 2011; Peters et al., 2009; Renaud, Bherer et Maquestiaux, 2010; Voelcker-Rehage, Godde et Staudinger, 2010; Voss, Erickson, et al., 2010). A recent review exploring the association among physical activity, cardiorespiratory fitness, and exercise on gray matter volume in older adults reinforced the link between higher cardiorespiratory fitness levels with greater gray matter volume in the prefrontal cortex, and highlighted the association with the hippocampus volume (Erickson et al., 2014). Furthermore, cardiorespiratory fitness levels have recently been associated with the size of the basal ganglia (Verstynen et al., 2012), but further studies need to be conducted as investigations are at their infancy.

Interventional studies have also demonstrated the effect of exercise on the aging brain. (Ballesteros, Kraft, Santana et Tziraki, 2015; Bherer, Erickson et Liu-Ambrose, 2013a; Colcombe et al., 2004; Erickson et al., 2014; Kramer, Erickson et Colcombe, 2006; Langlois et al., 2013; Renaud, Maquestiaux, Joncas, Kergoat et Bherer, 2010; Voelcker-Rehage, Godde et Staudinger, 2011). Once again, the aging and exercise literature have shown positive effects of exercise on brain structure, function and cognition. For instance, in a randomized control-trial with 120 older adults, Erickson et al. (2011) studied the effect of a chronic program of aerobic exercise at moderate intensity (three times a week for six months) on seniors' brain. A change in fitness levels was associated with an increased size of hippocampus (2%), and this change was correlated at the behavioural level by a significant improvement in spatial memory. The increased hippocampal volume was also associated with greater serum levels of brain derived neurotropic factors (BDNF), a mediator of neurogenesis in the dentate gyrus, but also a substance involved in exercise dependent plasticity (Gomez-Pinilla, Zhuang, Feng, Ying et Fan, 2011). This suggests that chronic aerobic exercise in seniors is able to prevent cognitive impairment and even reverse hippocampal volume loss normally seen in late adulthood.

Although there is a significant amount of evidence supporting the benefits of exercise on the brain, and specifically on cognitive abilities, there is still a paucity of literature to determine exercise-dependent changes on other types of brain functions, such as motor learning. We know that motor learning in seniors is preserved (Bennett, Madden, Vaidya, Howard Jr et Howard; King, Fogel, Albouy et Doyon, 2013; Rieckmann, Fischer et Backman, 2010), and somehow affected in PD (Dan, King, Doyon et Chan, 2015; Muslimović et al., 2007; Siegert et al., 2006; Werheid, Zysset, Muller, Reuter et von Cramon, 2003), but to our

knowledge our articles are the first studies to present results on the effect of exercise on cognitive and motor learning processes.

In PD, studying the effect of aerobic exercise on the motor system seems obvious. Epidemiologic evidence suggests that moderate exercise may act as a protective factor in PD (Chen, Zhang, Schwarzschild, Hernan et Ascherio, 2005; Hirsch et al., 2016; Xu et al., 2010). Animal studies also demonstrate a neuroprotective effect following vigorous exercise in rodent models of parkinson's disease by inducing brain neurotrophic and glial-derived neurotrophic factors expression, and by promoting angiogenesis or compensatory strategy to dopaminergic loss (Al-Jarrah, Jamous, Al Zailaey et Bweir, 2010; Fisher et al., 2008; Huang et al., 2012; Lau, Patki, Das-Panja, Le et Ahmad, 2011; Shin et al., 2016; Smith et Zigmond, 2003; Vucckovic et al., 2010; Wang, Guo, Myers, Heintz et Holschneider, 2015a; Wang, Guo, Myers, Heintz, Peng, et al., 2015; Yoon et al., 2007). To our knowledge, no studies in neuroimaging have been conducted to underlie the effect of cardiovascular exercise in PD despite strong evidence of brain plasticity in the elderly and chronic population.

Structures and functions of the brain modified by chronic exercise have been explained by four major neurophysiological mechanisms: 1) cortical vascularization (increased cerebral perfusion and blood flow; phenomena called angiogenesis), 2) synaptic plasticity (cerebral connectivity network modifies itself by creating new connexion, called synaptogenesis, or by reinforcing actual connexions due to new sensory and motor experiences), 3) neurogenesis (creation of new neuron in cerebral connectivity network, mostly observed in the dentate gyrus and hippocampus), 4) cerebral catecholamine or dopaminergic hypothesis changes release of dopamine and noradrenaline leading to more efficient dopaminergic central

receptors (Audiffren et al., 2011; Ryan et Nolan, 2016; Svensson, Lexell et Deierborg, 2015). These four neurophysiological hypotheses are hypothetically supported by the same molecular mechanism known as the neurotrophic hypothesis. Release of neurotrophins, due to chronic exercise would increase cerebral plasticity, mainly by participating in angiogenesis, synaptogenesis, neurogenesis, and neurotransmitters' synthesis. The three major neurotrophins involved in exercise dependent plasticity are Brain-Derived Neurotrophic Factor (BDNF), vascular endothelial-derived growth factor (VEGF) and Insulin-Like Growth Factor 1 (IGF-1). In PD, the dopaminergic (changes in the release) hypothesis seems intuitive, as we know, the undeniable implication of this neurotransmitter in the progression of the disease. Moreover, exercise can induce synaptic plasticity in the CS and CC systems, as we are aware of an existing compensatory mechanism in PD.

Although different types of exercise exist (e.g. resistance training, flexibility, coordination), aerobic training has shown the most unequivocal effects on brain health across the life span (Prakash, Voss, Erickson et Kramer, 2015; Voss et al., 2011). To date, this form also seems to have the most positive effect in PD by improving physical functioning, health-related quality of life, functional capacities and motor performance (Ahlskog, 2011; Gracies, 2010; Monteiro et al., 2016; Shu et al., 2014; Speelman et al., 2011b) while having also a promising effect on improving the NMS of PD (Reynolds, Otto, Ellis et Cronin-Golomb, 2016). Nevertheless, to our knowledge, no studies have investigated the effect of such treatment on motor learning and executive functions in PD. Hence, this thesis aimed to fill the gap in the literature by investigating the effect of aerobic exercise on cognition and motor learning in PD. Specifically, we have been interested to study the impact of aerobic exercise on executive

functions, such as inhibition and flexibility, as measured by reliable and valid cognitive tasks, the Stroop and the Trail making (A and B) tests. Most importantly, we studied the effect of aerobic exercise on motor skill learning in PD, and identify the neural correlates involved in an implicit motor sequence learning task (SRTT).

3. Thesis's Aim and Hypotheses

The principal aim of the present thesis was to investigate the effects of cardiorespiratory (VO_2max and maximal aerobic power) exercise in PD patients on cognition (neuropsychological testing) and motor learning (SRT-fMRI), and then to identify the neural substrates mediating the effects of exercise on motor sequence learning. Secondary outcomes included functional capacities (United Parkinson's Disease Rating Scale, UPDRS) and other health indicators (blood pressure, weight, heart rate). We determined: 1) whether 3 months of aerobic exercise training (AET) improves results of VO_2max and maximal aerobic power in PD and in healthy control (HC), 2) whether 3 months of cardiorespiratory training increase cognitive abilities (executing functions) in PD and in HC, 3) whether 3 months of AET ameliorates the learning of a new motor sequence of finger movements in PD and HC, and 4) the neurofunctional mechanisms mediating the effects of AET on motor sequence learning (MSL). Specifically following Doyon's model of MSL, we verified whether AET improves MSL through augmented activity in the cortico-striatal (CS) system or via a compensatory mechanism involving the cortico-cerebellar (CC) system, and 5) whether the improvements following AET in PD were specific to the aerobic nature of the training program.

Chapter II: Articles

Article 1: Enhancing both motor and cognitive functioning in Parkinson's disease: Aerobic exercise as a rehabilitative intervention

Statement of contribution for all authors:

Catherine Duchesne: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision

Ovidiu Lungu: Analysis and interpretation of data, drafting of manuscript, critical revision

Alexandra Nadeau: Acquisition of data, analysis and interpretation of data, critical revision

Marie-Ève Robillard: Acquisition of data, critical revision

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Louis Bherer: Analysis and interpretation of data, critical revision

Julien Doyon: Study conception and design, analysis and interpretation of data, drafting of manuscript, critical revision

Published: *Brain and Cognition*

TITLE: Enhancing both motor and cognitive functioning in Parkinson's disease: Aerobic exercise as a rehabilitative intervention

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ABSTRACT

Background: Aerobic exercise training (AET) has been shown to provide health benefits in individuals with Parkinson's disease (PD). However, it is yet unknown to what extent AET also improves cognitive and procedural learning capacities, which ensure an optimal daily functioning. **Objective:** In the current study, we assessed the effects of a 3-month AET program on executive functions (EF), implicit motor sequence learning (MSL) capacity, as well as on different health-related outcome indicators. **Methods:** Twenty healthy controls (HC) and 19 early PD individuals participated in a supervised, high-intensity, stationary recumbent bike-training program (3 times/week for 12 weeks). Exercise prescription started at 20 minutes (+5 minutes/week up to 40 minutes) based on participant's maximal aerobic power. Before and after AET, EF tests assessed participants' inhibition and flexibility functions, whereas implicit MSL capacity was evaluated using a version of the Serial Reaction Time Task. **Results:** The AET program was effective as indicated by significant improvement in aerobic capacity in all participants. Most importantly, AET improved inhibition but not flexibility, and motor learning skill, in both groups. **Conclusion:** Our results suggest that AET can be a valuable non-pharmacological intervention to promote physical fitness in early PD, but also better cognitive and procedural functioning.

Key Words: Parkinson's disease, aerobic exercise, cognition, motor, executive functions, procedural learning ***(6)***

Word count: Abstract (199); Text (6179)

1. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder, which manifests through motor symptoms including tremor, rigidity, slowness of movement (bradykinesia) and gait difficulties. Neuropathologically, PD is a multisystem disorder characterized not only by nigrostriatal dopaminergic cell loss in the basal ganglia, but also by disorders of mesocortical dopaminergic, noradrenergic, and other systems (Jellinger, 2012). These lesions lead to disruptions of motor program selection by the striatal circuitry, affecting in turn, the entire cortico-striatal system (Amano, Roemmich, Skinner et Hass, 2013), and individuals' motor learning capacity (Stefanova, Kostic, Ziropadja, Markovic et Ocic, 2000). In addition, there is evidence that degeneration in PD is present in multiple systems even from the onset, as it can be observed in early cognitive dysfunction, mainly in processes and tasks that require executive functions, abilities directing and coordinating the execution of human behaviours (Kudlicka, Clare et Hindle, 2011). As a result, cognitive dysfunctions aggravate motor symptoms, and in turn compromise activities of daily living and the quality of life (Dirnberger et Jahanshahi, 2013). Overall, the heterogeneous nature of the disease raises difficulties in finding treatments to alleviate these multicomponent manifestations. Thus, much effort is devoted nowadays to researching complementary, non-pharmacological interventions, which can help improve both motor and cognitive symptoms of PD. Physical exercise constitutes such an alternative intervention.

Among many different types of physical exercising (e.g., resistance training, flexibility, coordination etc.), aerobic exercise training (AET) has been the most studied and has shown unequivocal health benefits across the life span (Voss et al., 2011), as well as in different clinical

populations, such as PD. Specifically in PD, AET has been found to improve physical functioning, quality of life, and functional capacities (Ahlskog, 2011; Goodwin, Richards, Taylor, Taylor et Campbell, 2008; Gracies, 2010; Herman et al., 2009; Nadeau, Pourcher et Corbeil, 2014; Petzinger et al., 2013a; Speelman et al., 2011b). For instance, progressive treadmill training has revealed mobility gains following 6 weeks of AET, resulting in improvements in both activities of daily living and quality of life in people with PD (Herman et al., 2007). Another cardiorespiratory exercise study in the same population has demonstrated improvements in motor functions and bimanual dexterity after only two months of intense supervised bicycle training (Ridgel et al., 2009). While much work has been done to show the benefits of AET on functional capacities in PD, such as gait, the evidence for such an effect on cognition and motor learning capacity is still scarce (Murray, Sacheli, Eng et Stoessl, 2014). Furthermore, additional investigations are still needed to demonstrate that such treatment can benefit cognition and motor functioning in parallel, and to identify the underlying brain mechanisms by which AET benefit PD individuals in both areas.

There is now overwhelming evidence that the adult brain is very plastic and that this cerebral plasticity is maintained or increased through exercise in elderly and other frail populations (Bherer et al., 2013b). The structural and functional changes produced by chronic exercise have been explained by various neurophysiological mechanisms, including the synaptic plasticity (e.g., synaptogenesis, reinforcing the existing connexions due to repeated associations between new sensory and motor experiences) and a change in dopaminergic neurotransmission (Audiffren et al., 2011). Given that the latter mechanisms suggest the existence of a connection between the brain circuitry involved in PD (i.e., dopaminergic) and

exercise-dependent cerebral plasticity, it is conceivable that this type of non-pharmacological interventions could preserve, or help restore motor and cognitive effectiveness in PD. Nevertheless, to our knowledge, no study has investigated the effect of exercise on both procedural motor learning and executive functions in PD, despite the remarkable overlap between the neuropathology of PD, and the neuronal correlates associated with exercise dependent plasticity (Petzinger et al., 2013a).

To date, physical exercise literature reports similar effects of training in healthy older adults and PD patients (Audiffren et al., 2011; Bherer et al., 2013b; Murray et al., 2014). Hence, the principal aim of the present study was to investigate the effects of cardiorespiratory exercise in both PD and healthy controls (HC) on cognition and motor learning, as well as to explore these effects within each group. Specifically, we hypothesised that 3 months of progressive intense aerobic exercise training (AET) would improve significantly and in a similar fashion in both groups, hence helping to normalize PD patients' performance in: 1) aerobic capacity 2) cognitive abilities (specifically executing functions such as inhibition and flexibility), and 3) procedural motor learning.

2. METHODS

2.1. Participants

A total of 39 women and men divided into two groups (19 PD patients and 20 HC aged between 40 and 80 years old) participated in the present study. Demographic characteristics of the samples are presented in Table 1. Participants were assigned to a 3-month, supervised (i.e., with trained kinesiologists) AET program in small groups of four participants per trainer.

Study inclusion criteria specific to PD individuals were the following: patients had to be classified as stage 1 or 2 according to Hoehn and Yahr's scale (Hoehn et Yahr, 1967) based upon neurological evaluation, and had to score below 35 on motor functions assessed with the United Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008). Study inclusion criteria for both PD and HC participants were based on screening tests for dementia. Specifically, to be eligible they needed to score 24 or more on the Mini Mental State Evaluation (Folstein, Folstein et McHugh, 1975) or on the Montreal Cognitive Assessment (Marinus, Verbaan et van Hilten, 2011) tests. In addition, eligible participants had to be sedentary at baseline (a score of 5 or lower on the Jackson's Questionnaire) (Jackson et al., 1990). As a result of our selection process, the two groups were matched on sex distribution, age, and years of education, in addition to cognitive and fitness levels.

2.1.1. Cognitive and motor assessments

2.1.2. Executive functioning

Two neuropsychological executive tests measuring inhibition and flexibility abilities were administered both before and after AET in the current study (Spreen, 2006). First, participants' inhibitory aptitude was evaluated using a version of the Stroop test with three different conditions (reading, naming, and inhibition). Each of these conditions was composed of 100 stimuli (i.e., words, coloured rectangles, words in colours) printed on a 21.5×28 cm sheet of paper. In the reading condition, participants had to read the words (red, green, blue, and yellow) printed in black. In the naming condition, subjects needed to name the colour of the rectangles. Finally, in the interference condition, individuals were asked to name the colour

of the ink in which the words were written. In the latter condition, the meaning of each word had to be ignored, as it was incongruent with the colour to name (e.g., the word “green” written in red). Second, the Trail Making test (TMT) was then used to measure subjects’ flexibility functions. The test has two parts, TMT A and TMT B, administered in this order. The TMT A included numbers from 1 to 25, circled and written on a 21.5×28 cm sheet of paper. Participants were asked to connect with a pencil, as fast as possible, the numbers in numerical order. By contrast, TMT B included numbers from 1 to 13 and letters from A to L. This time, subjects were required to connect, as fast as possible, a number followed by a letter in numerical and alphabetic order, respectively.

2.1.3. Motor sequence learning

Subjects’ implicit MSL capacity was evaluated using a version of the serial reaction time (SRT) task, in which participants were asked to press one of the four buttons on a keyboard in response to four horizontally aligned visual stimuli presented on a screen (Nissen et Bullemer, 1987b). Participants had to react as fast and accurately as possible to the location of the stimulus by pressing the spatially corresponding key, with left and right index and middle finger. In our version of the task, stimuli were presented at random or in a repeating sequential order, in blocks of 40 stimuli each. These blocks were presented in triplets (Sequence, Random, Sequence; see Figure 1), for a total of 12 triplet conditions during the entire session. For the sequential blocks, two 8-item, second order conditional sequences (2-4-3-1-4-2-1-3 and 3-1-2-4-1-3-4-2) were used and counterbalanced between sessions (pre-, post-AET) and subjects to avoid repetition of the learned sequence for the same individual. The two sequences were identical both in terms of the frequency of each finger response and transition from one

element to another. To reduce subjects' awareness about the sequence, each sequential block started at a random point in the sequence. For each trial, reaction time (i.e., the time between the onset of the stimulus to the completion of the response) and accuracy (i.e., correct element within the sequence) were recorded. To assess sequence learning, RTs and accuracy were compared between the sequence and random blocks, with faster RTs and better accuracy for sequence as compared to the random blocks reflecting the procedural motor learning capacity.

2.1.4. Physical fitness

Participants' physical fitness level was evaluated using either a submaximal aerobic test (11 HC, 5 PD) or a medically supervised oxygen consumption test (9 HC, 14PD). The protocol required a five minutes resting period before measuring their heart rate, blood pressure, and aerobic capacity. Participants evaluated with a sub-maximal test (recumbent bike) started with a workload stage of 35 or 50 Watts (W), for women or men, respectively, lasting one minute; the intensity progressively increased by 15W every minute until they reached 85% of their predicted maximal heart rate (HRmax = 208-0.7*age). When the target heart rate was reached, participants were asked to complete the current stage (if possible). The power level (in W) of the last completed stage was used to extrapolate the maximal aerobic power (MAP). Then, VO_2max estimation was calculated with body weight (kg) and MAP (W) measures, using the American College Sport Medicine's formula: VO_2 = (10,8*Watts/weight) + 7 (Marsh, 2012); MAP estimation was used for exercise prescription. For the participants evaluated with a graded cycling (one minute workload stage) maximal test, the protocol started, similarly, at 35W for women (50W for men), and the intensity progressively increased by 15W every minute until maximal efforts criteria were fulfilled (e.g., age predicted maximal heart rate +/-

10 bpm and VO_2 plateau or until subjects could not maintain the required workload (fatigue). Aerobic capacity (VO_2peak) was measured directly using a breath-by-breath system. The last completed stage power (W) was recorded and used for exercise prescription (Mailey et al., 2010; McAuley, Szabo, Mailey, Erickson, Voss, White, Wojcicki, et al., 2011). Importantly, PD individuals performed the stress test while following their usual medication regimen, which did not change during the study period. Also, for each patient, the stress tests were administered at the same time of day and did not change pre-to-post AET.

2.1.5. Other measurements

Other physical health measurements included weight, heart rate and blood pressure. Psychological health variables (depression and anxiety) were also assessed using the Beck Depression Inventory (BDI) (Beck et Beamesderfer, 1974) and Beck Anxiety Inventory (BAI) (Osman, Kopper, Barrios, Osman et Wade, 1997), respectively.

2.2. Experimental design

We used a repeated measures design, with all participants being assessed both pre- and post-training, 3 months apart. Prior to participation, each individual was informed in details about the study protocol before signing the study consent form, which was approved by the “Regroupement Neuroimagerie Québec” Ethics Review Board.

2.2.1. Procedure: Evaluations at baseline and follow-up

Each evaluation session started with physical and cognitive assessments (described above), which took part over the course of a day. Then, two days later, participants were tested on their abilities to acquire a motor sequence using the implicit learning paradigm. To this end,

they performed the SRT task described above while lying supine in a 3.0 Tesla TIM TRIO Siemens scanner and having their brain activity recorded. Given our objectives, we report here only the data related to behavioural performance on the motor learning task and neurocognitive tests.

At the end of the SRT task, a process dissociation procedure (PDP) was used to probe participants' awareness about the sequence (Destrebecqz et Cleeremans, 2001). Participants were asked the following questions: "Did you use a particular strategy to perform the task?" and 'Did that strategy change during the task?". To preserve the implicit nature of the task in the pre-AET evaluation session, more detailed questions were administered to the participants only in the post-AET evaluation session. These were: "How would you best describe the responses given during the experiment: 1) random, 2) the succession of responses was often predictable (if so, when?), 3) the same sequence was repeated throughout the task (if so, when?)" (Curran, 1997). Next, participants were informed about the presence of a repeating sequence and asked to recall that sequence by pressing a series of 36 responses. They were first asked to produce a sequence that resembled the trained sequence as much as possible (free recall under inclusion condition). They were then instructed to produce another sequence that differed as much as possible from the trained sequence (free recall under exclusion condition) (Destrebecqz et Cleeremans, 2001). The proportion of triplets (e.g. three consecutive elements) consistent with the sequence, under inclusion and exclusion instructions, was then computed. As such, an index of sequence awareness was obtained by computing the difference between performance under inclusion and exclusion instructions. Participants having a high inclusion score (i.e., that were able to correctly recall the trained

sequence) and a low exclusion score (i.e., that were able to refrain from that sequence by generating a different one) were thought to have some conscious (explicit) awareness of the sequence. Yet using such a measure, the results revealed that none of the participants was aware of the repeating sequence; hence suggesting that the protocol allowed us to measure, as intended, subjects' capacity to implicitly learn a new sequence of movements.

2.2.2. Procedure: The exercise protocol

The cardiorespiratory fitness program involved three months of recumbent bike-training, three times a week, 1 hour/session, which occurred at the same time of day. The exercise intensity prescription was based on the subject's maximal aerobic power output from the maximum volume of oxygen (VO_2peak) uptake conducted on pre-test day (American College of Sport Medicine, 2006; Canadian Society for Exercise Physiology, 1996). Duration of the exercise program started at 20 minutes and 60% of intensity per session, and was then increased by steps of 5 minutes and 5% of intensity every week until participants reached 40 minutes of training at 80% intensity. To reach a high-intensity level, bike speed was maintained at 60 revolutions per minute (RPM). As such, to achieve the desired bike resistance power and adjust intensity level (if needed), the work intensity was based on power output (Watt), controlling for subject's heart rate. In addition, rate of perceived exertion (Borg scale) (Borg, 1982) was assessed on each training session. The target of 75% or more in participation rate in the fitness training program was achieved. In addition, PD individuals did not change their medication regimen for the entire duration of the study.

2.2.3. Statistical Analysis

The main independent variables included in our analyses were the presence/absence of the disease (i.e., PD vs. HC groups) and the effect of aerobic training, expressed as the time of testing (pre- vs. post- intervention, within-group independent variables). Dependent variables included the following: physical fitness (expressed as VO_2max estimate), physiological measures (heart rate at rest, blood pressure), results on the cognitive tests (Stroop, TMT), and the subject's performance (i.e., execution speed, learning score) on the MSL task. We first assessed the relationship between independent and dependent variables using a mixed repeated measures analysis of variance (ANOVA), with group as between-subjects factor and time of testing as within-subjects factor. In order to account for the effect of multiple comparisons, the statistical significance was adjusted using the Bonferroni method. We also conducted a correlation analysis in order to assess the relationships between cognitive and motor skill measurements. All analyses were performed with SPSS 20 (IBM Inc, Armonk, NY).

3. RESULTS

No significant difference between groups were found at baseline with respect to sex distribution and mean age, as well as to their levels of education, fitness, and cognitive functioning; hence reflecting that the two groups were well matched prior to the AET intervention program. Yet, significant group differences were found on depression and anxiety questionnaires (see Table 1). Therefore, both of these variables were considered as covariates in all subsequent analyses. Table 2 presents the results for all physical and cognitive measures pre- and post-AET.

3.1. Aerobic exercise training and physical fitness

There was no significant group x time of testing interaction, nor any group differences with respect to all physical measures. As expected, however, the 3-months aerobic training regimen yielded a significant improvement in aerobic capacity (the estimated VO_2max) in the two groups combined ($F_{1,35}$=17.33, p<0.001) with a clear tendency for the PD patients to show level of post-training fitness similar to the one observed in matched elderly subjects prior to the training regimen. A significant improvement was also observed separately in both HC ($F_{1,35}$=15.19, p<0.001) and PD ($F_{1,35}$=9.98, p<0.003) groups. The estimated power level increased significantly in the HC ($F_{1,35}$=14.93, p<0.001) and PD ($F_{1,35}$=10.50, p<0.003) groups following AET. The systolic blood pressure improved significantly when the two groups were combined together ($F_{1,35}$=4.66, p<0.038) and for the HC group ($F_{1,35}$= 17.35, p<= 0.001), but only reached marginal significance for the PD individuals ($F_{1,35}$=3.45, p=0.072). No such effect was observed when looking at the measure of diastolic blood pressure. In addition, the HC group (but not the PD group) showed a significant weight loss after AET ($F_{1,35}$= 5.56 p<0.024), with no significant effect when combining the two groups. Heart rate at rest improved significantly in PD patients ($F_{1,35}$=4.59, p<0.039) and when both groups were combined ($F_{1,35}$=6.81, p<0.013), but was only marginally significant in the HC individuals ($F_{1,35}$= 3.04, p=0.09). Altogether, these results indicate that the effect of exercise had similar physiological benefits in both groups and mostly increased significantly individuals' aerobic capacity.

3.2. Aerobic exercise training and cognition

The 3-months of AET regimen yielded a significant improvement on the Stroop inhibition condition measure, both when groups were combined ($F_{1,35}$=5.49, p<0.025), and separately for the HC ($F_{1,35}$=5.52, p<0.025) and PD groups ($F_{1,35}$= 7.82, p<0.008). The other cognitive measures (i.e., Stroop: reading and naming conditions, Trail Making A and B) did not show any statistically significant changes following the AET program. Again, no significant interaction, or group difference was found in regards to all of these cognitive measures.

3.3. Effects of aerobic exercise training on motor sequence learning

When combining the two groups (HC and PD), we observed a significant training-related effect on motor execution, regardless of the movement type (sequence vs. random). Specifically, all participants improved their speed of movement execution after AET ($F_{1,35}$=7.16, p<0.05). Also regardless of the time of testing (i.e. pre- vs. post-AET) there was a significant difference in reaction time between sequential and random movements ($F_{1,35}$=17.71, p<0.001), with movements during the sequence being faster than during the random condition; an indicator of implicit motor sequence learning capacity. In addition, there was a marginal interaction effect between movement type and time of testing ($F_{1,35}$=3.65, p=0.064), hence suggesting that procedural learning capacity tended to improve following AET when both groups were combined.

In regards to training-related motor execution improvements in each group, separately, we observed an increase in execution speed for both sequence ($F_{1,35}$=12.53, p<0.001) and random movements ($F_{1,35}$=8.42, p<0.006) in HC participants, whereas PD individuals showed AET-related improvement only in regards to the sequential movements ($F_{1,35}$=5.17, p<0.029).

Furthermore and more importantly, when assessing motor sequence learning capacity in each group, we identified a significant procedural learning effect (i.e. faster execution of sequential versus random movements) pre-AET in HC ($F_{1,35}$=4.06, p=0.052), but not in PD ($F_{1,35}$=1.43, p=0.24). After training, however, both groups showed significant learning effects ($F_{1,35}$=7.13, p<0.011, for HC and $F_{1,35}$=8.88, p<0.005 for PD).

Finally, partial correlation analyses (controlling for anxiety and depression levels) revealed that cognitive (inhibition and flexibility) and motor skills (motor sequence and random conditions) were highly correlated both pre- and post-exercise, when both groups were analyzed together (all positive correlations, p<0.01). However, a detailed analysis of such correlations revealed that these effects were driven by data originating solely from the PD group. Specifically, cognitive abilities were significantly and positively associated with motor skills, both pre- and post-AET, in the PD patients only. Furthermore, the same type of partial correlation analysis (controlling for anxiety and depression levels) also revealed that, in PD patients, the baseline cognitive performance was positively associated with AET-related improvement (within both the inhibition - p<0.05 and flexibility - p<0.005 domains), whereas the baseline motor learning performance was negatively associated with training-related improvements in motor learning capacity (p<0.005). In controls, only the initial motor performance was significantly and negatively associated with the AET-related improvement (p<0.01); their baseline cognitive performance was not predictive of training-related changes in the cognitive domain.

4. DISCUSSION

This study demonstrates that cardiorespiratory fitness can be significantly improved in both HC and PD participants after only 3 months of progressive supervised aerobic exercise training. Interestingly, the level of fitness achieved by PD patients after training was similar to the one the healthy elderly subjects started with. As predicted, our results also reveal that AET produced beneficial effects on cognitive and motor learning skills in the two groups. Specifically, we observed AET-related improvements in participants' inhibitory aptitudes, but no statistically significant changes in cognitive flexibility in either group. In the motor domain, the 3-month exercise regimen ameliorated participants' procedural learning capacity (i.e. difference in performance between sequential and random movement execution) in both groups. More importantly, while HC subjects increased their performance in both random and sequence conditions, AET specifically improved the PD patients' ability to acquire implicitly a new motor sequence. Furthermore, AET was particularly beneficial for PD as the implicit procedural learning effect was evident only following the exercise training program. Finally, our findings also demonstrate the existence of a relationship between cognitive and motor functions in individuals with PD only, both before and after AET. The baseline performance in the PD group was differentially associated with training-related improvements in both cognitive and motor domains.

The hypothesis that AET would ameliorate executive functions (inhibition and flexibility) in both PD and matched elderly individuals was only partially confirmed in the present study, as we found significant improvements only in regard to inhibition (Stroop test), but not flexibility (Trail Making Test - TMT). The lack of effect of physical exercise on flexibility could be attributed to the motor component of the trail making task that augment task

difficulty in PD patients. Yet, our results suggest that this is not necessarily the case, for two reasons. First, the flexibility score was obtained by subtracting the execution time from the two test conditions (TMT B vs. TMT A), hence eliminating the motor execution confound. Second, we found no significant training-related improvement in this type of executive function in matched HC controls, either. Although unexpected, such a pattern of findings is in line with the extant literature on physical exercise in older adults, given that previous studies have also yielded inconsistent findings regarding significant improvements in specific executive functions, such as flexibility or inhibition. For instance, a meta-analysis of 29 randomized control trials (RCT), published between 1966-2009, on aerobic exercise and neurocognitive performance (Smith et al., 2010) concluded that aerobic exercise in elderly subjects is associated with modest improvements in cognitive functions. They established that substantial heterogeneity among cognitive measures (e.g., variety of tests used to measure executive function) and exercise (e.g., various time duration) contributed to the ambiguity of results. Yet, several recent studies (after 2009) that used these neuropsychological tests (Stroop and TMT) before and after an aerobic exercise program, similar to the design implemented in our study, have demonstrated analogous profiles of results. (Langlois et al., 2013; Liu-Ambrose, Nagamatsu, et al., 2010; Predovan et al., 2012). For instance, Predovan and colleagues (Predovan et al., 2012) have reported gains in performance in the inhibition/switching condition of the Stroop task in healthy elderly individuals after a 3-month exercise program composed of stretching and cardiorespiratory exercises (i.e., fast walking and aerobic dancing). Finally, Langlois and colleagues reported improvements in executive functioning (composite score based on equally weighted Stroop and TMT z-scores) after 12 weeks of aerobic exercise

training in the intervention, but not in the control group (waiting list), both groups being composed of frail and non-frail elderly participants. Overall, the evidence from the literature on physical exercise and cognition in healthy older adults seems to indicate that chronic aerobic exercise training improves executive functions, in general. Yet, more studies are needed to elucidate the extent to which aerobic exercise has stronger and more specific effects in improving the inhibition (as measured by Stroop test), rather than flexibility function (as measured by TMT) in this population.

The literature on physical exercise and cognition in Parkinson's is less abundant. A systematic review (Murray et al., 2014) on randomized and non-randomized trials, covering the period 1966-2013, revealed only four studies which have specifically evaluated the effect of physical exercise on executive functions in patients with PD (Cruise et al., 2011; McKee et Hackney, 2013; Ridgel, Kim, Fickes, Muller et Alberts, 2011; Tanaka et al., 2009). Unfortunately, however, none of these studies used the Stroop test, but one (Ridgel et al., 2011) employed the TMT and found a significant improvement in the flexibility score (difference in reaction time between TMT B and A) after acute bouts of AET in PD using passive leg cycling. Specifically, the authors provided evidence that 3 sessions of 30 minutes of AET improved flexibility in PD. In addition, one recently published RCT reported no significant difference in Stroop inhibition and TMT flexibility scores in 49 PD patients following a 6-month aerobic exercise regimen (Uc et al., 2014). It is noteworthy to mention, however, that duration, intensity and type of training used in these studies were different from those in our design, in which we focused on chronic high intensity cycling rather than on a moderate intensity exercise (i.e., fast walking). In summary, the PD literature on physical exercise and executive function is scarce and the

evidence indicating a positive effect is moderate, at best. In addition, further research is needed to identify factors that can contribute to these effects. One possibility is that the duration of training (chronic vs. acute) and intensity (intense vs. moderate) play an important role in the amount of gains seen in cognitive functioning, as well as in the specificity of cognitive improvement (inhibition vs. flexibility) that one will observe in PD individuals. To this end, our findings provide, for the first time, evidence that chronic and intense aerobic exercise can improve cognitive inhibition skills in PD, as measured through the Stroop test. More importantly, we showed that this effect is not specific to this population; instead, it is seen in both elderly PD and healthy individuals.

It is important to note that, in the current study, we specifically selected PD patients with no cognitive impairment in order to match them with healthy control subjects and that the two groups did not differ in terms of their levels of performance on executive tasks at baseline. Thus, despite consistent evidence that PD are typically impaired on tests of executive functioning (Kudlicka et al., 2011), our study is also the first to provide evidence that cognitively unimpaired PD individuals benefit from AET to the same extent, and in a similar manner, as the matched healthy controls (i.e., only inhibition and not flexibility). This assertion is further supported by the fact that we found no significant interaction (group*time of testing) or group differences in regards to either of the cognitive variables (inhibition and flexibility), indicating that the aerobic exercise had, indeed, similar effects among sedentary older HC and cognitively unimpaired PD individuals.

In sum, our findings suggest that AET-related improvements in executive function in cognitively intact early PD patients could be based on similar neurophysiological mechanisms

as those described in healthy older adults (Bherer et al., 2013b). Indeed, there is evidence that the benefits of aerobic exercise on executive functions, as well as on memory (e.g. working and spatial memory) in the elderly, are accompanied by transient, as well as permanent brain changes at both structural and functional levels. For instance, Erickson and colleagues (Erickson et al., 2011) have reported an increase in hippocampal volume, which was related to improved spatial memory function following aerobic training in the elderly population, whereas Colcombe et al. (Colcombe et al., 2004) have provided evidence that brain regions in the attentional network were more active in highly fit and aerobically trained individuals. One year of moderate aerobic training in older adults has also been found to improve functional connectivity between regions that typically show age-related disruptions (Voss, Prakash, et al., 2010). Finally, a high cardiorespiratory fitness level has been associated with a reduced age-related loss of grey and white matter in the frontal, prefrontal, and temporal regions in older adults (Colcombe et al., 2003), whereas the caudate nucleus volume has been thought to mediate the relationship between the level of cardiorespiratory fitness and task switching performance in older healthy adults (Verstynen et al., 2012). Given the fact that systematic literature reviews report similar effects of physical exercise on cognition in both healthy elderly and PD (Ahlskog, 2011; Bherer et al., 2013b; Murray et al., 2014; Petzinger et al., 2013a), it is thus conceivable that similar functional and structural changes in the brain may constitute the basis for the cognitive improvement in both HC and PD. Yet, future neuroimaging studies using an experimental design similar to ours will be needed to elucidate this issue.

In addition to the brain structural and functional mechanisms described above, the benefits of physical exercise on cognitive functions might also be due to improvements from

indirect action mechanisms (Petzinger et al., 2013a). For instance, Spirduso and colleagues (Spirduso, Francis et MacRae, 2005) have suggested that AET may enhance cognition by improving health conditions (i.e., decreasing stress and sleep difficulties) and by reducing chronic diseases (e.g. inflammation, coronary heart diseases) that also impact neurocognitive functions. Indeed, it has been shown that physical exercise enhances mental resources by reducing depression (Bartholomew, Ciccolo, Spirduso, Poon et Chodzo-Zajko, 2008), anxiety, and chronic stress while improving self-efficacy (McAuley, Elavsky, Spirduso, Poon et Chodzo-Zajko, 2008). In the present study we observed an improvement in physical fitness, as well as in other health indicators (i.e. systolic blood pressure, heart rate at rest) in our participants after AET. Yet it is difficult to assess whether the pattern of results on the inhibitory and flexibility tasks reported here is related or nor to this type of indirect effects, as only epidemiological studies with large cohorts could confidently measure and link physical exercise with these health conditions. Furthermore, although we did not find any change on measures of anxiety and depression pre- versus post-AET in our participants, our results revealed some heterogeneity between groups on these psychological variables, and PD patients showed greater signs of anxiety and depression compared to their healthy counterparts. Consequently, it is possible that differences on these psychological factors might have influenced the pattern of results observed on the inhibitory and flexibility measures of cognition reported here. Indeed, there is evidence that such psychological symptoms can mediate the participant's level of self-efficacy and motivation to maintain their efforts during physical training, such as one's belief in his or her capabilities to overcome personal, social, and environmental barriers to exercising (Ellis et al., 2011). Such factors are also associated with poorer executive functions

in older adults (Beaudreau et O'Hara, 2009; Johnco, Wuthrich et Rapee, 2015). Yet, we believe that our findings are not due to such confounding variables because: 1) the effects of AET on cognition were observed in both groups, and not only in PD patients, and 2) most importantly, we did control for the possible effects of such psychological variable in our analyses by considering the participants' level of anxiety and depression as covariates.

The other primary outcome in our study was that the procedural learning capacity improved significantly in PD following AET. A recent meta-analysis of 27 studies on motor sequence learning revealed that individuals with PD are impaired, as compared with healthy controls, in their ability to implicitly learn specific motoric sequential regularities through repeated practice (Clark, Lum et Ullman, 2014); a pattern that was replicated here prior to the aerobic training. Previous work on implicit MSL in PD patients has shown that many factors can affect procedural learning capacity, such as task complexity, learning stage, disease's severity, dopaminergic (DA) medication and sequence awareness (Gamble et al., 2014; Ruitenberg, Duthoo, Santens, Notebaert, & Abrahamse, 2015). Of these, we believe that task complexity, sequence awareness and learning stage could not play a role in explaining our results pattern given that these factors did not change as per our experimental design. In terms of disease severity, all our PD participants were in the early stage of the disease and their UPDRS scores also did not change significantly from pre- to post-training. Finally, the effects of DA medication are more difficult to assess. There is accumulating evidence that DA medication may improve the motoric aspects of the MSL task, while hindering the cognitive-related processes involved in it (Ruitenberg et al., 2015). Although our study design does not allow us to separate these two types of processes, we would nevertheless argue that DA medication

did not contribute in a major fashion to the modulation of AET-related effects seen in our study because the medication regimen or the time at which PD patients took their dose did not change during the entire study.

Nevertheless, consistent with our working hypothesis, we found that the AET improved significantly the procedural learning capacity in PD individuals, but not in healthy controls, hence suggesting that this effect may involve some alleviation of deficits in the dopaminergic system. Indeed, on the one hand, there is ample evidence that improved performance on a motor sequence learning task is mediated by plasticity in the cortico-cerebellar and cortico-striatal systems (Doyon et al., 2009; Doyon et Benali, 2005a). On the other hand, there is also evidence that aerobic exercise exerts influence on efficiency in dopaminergic neurotransmission within the basal ganglia (Petzinger et al., 2010). Accordingly, although still conjectural, one could hypothesize that the improvement in procedural learning following exercise observed in our PD individuals was due to plastic changes within the CS system. As such, exercise would drive activity dependent plasticity through mediation of the CS hyperactivity that is, in turn, modulated by dopaminergic signalling. Alternatively, one could also propose that the improvement in MSL after AET in PD is due to a compensatory mechanism via the cortico-cerebellar system. Further research using functional magnetic resonance imaging would allow the identification of neurophysiological mechanisms of plasticity by which aerobic exercise acts on the brain, and how it is associated with procedural learning performance in PD.

One other novelty from our study is the fact that AET-related effects on both motor skill learning and cognitive executive functions were simultaneously investigated. Despite

growing interest in investigating motor and cognitive functioning in PD patients who followed an aerobic exercise program (Murray et al., 2014; Petzinger et al., 2013a), no study had yet studied the effect of AET on both of these functions in PD. In this context, our results do not only reveal training-related improvements in the patients' abilities to learn a new sequence of movements or to improve their capacity in inhibiting non-relevant information, but also identify a positive relationship between both abilities in PD individuals. The latter findings are consistent with studies showing that the cortico-striatal dysfunction in PD is at the origin of the deficits observed in both executive cognitive functions and motor sequence learning (Fama et Sullivan, 2002; Sarazin et al., 2002). However, the fact that this positive correlation was observed not only before, but also after AET, combined with the training-related improvements in both inhibition function and motor sequence learning in PD, indicate: [1] that the correlation between motor and cognitive performance may be a sign of the neurodegeneration specific to PD and not to aging, and [2] that this relationship seems to be invariant of interventions delivered like physical exercise training. Furthermore, the baseline cognitive performance of PD individuals was positively associated with AET-related improvements in both flexibility and inhibition executive functions, with baseline motor performance (motor learning score) showing the opposite pattern.

Taken together, the results based upon correlations have important practical implications for the use of physical exercise as a non-pharmacological intervention in cognitively intact early PD. They suggest that PD individuals with poorer motor performance than their peers also tend to have poorer cognitive performance, both before and after physical exercise intervention. However, the effects of AET on cognition and motor learning

capacity will be different, depending on the initial baseline level. Individuals with poorer initial performance in both motor and cognitive domains will improve more in the motor, but less in the cognitive domain, whereas those with better initial performance will improve more on cognitive and less on motor area. As such, these findings should help define and personalise prescription of exercise treatment according to symptomatology.

Given the present results, it is conceivable that a non-pharmacological intervention, such as aerobic exercise, may preserve or restore cognitive and motor functions in Parkinson's disease. However, since most of our daily living activities involve the coordination of both cognitive and motor functions (e.g. cooking and dressing), it becomes important to explore further how cognitive and motor abilities relate with each other when performing these tasks. To this end, the present study establishes a relationship between cognitive and motor performance that seems to be specific to PD, revealing that the link between cognitive and motor brain functions in these individuals is probably dependent on the impairments in cortico-striatal system and subsequent brain reorganization, which may also be responsible for exercise-dependent plasticity.

5. CONCLUSION

In this study, we demonstrated that AET facilitates some executive functions and motor sequence learning, and thus appears to be an empowering mean to fight the motor and cognitive decline in PD. Similar to other investigations in this area, however, a limitation of our study is the heterogeneity of the patient population. Disease characteristics were diverse (e.g., motor, cognitive, neuropsychiatric, etc.) and it was often a challenge to control for all

symptoms and obtain a homogeneous sample. We used several strategies to address these limitations, however. First, we matched the PD group with the healthy control group with respect to sex distribution, age, years of education, cognitive and fitness level. In addition, given that the two groups differed in their symptomology of depression and anxiety, we accounted for these variables in our statistical analyses by considering them as covariates.

Furthermore, the present investigation was not set out to explore the exercise dose-response relationship, the level of change or protection provided by various types of exercise, or neurophysiological mechanisms underlying these effects in PD. Yet we believe that our study makes several important contributions to the field. First, we show that a 12-week progressive aerobic training regimen has beneficial effects on motor and cognitive skills in sedentary PD and healthy individuals. Second, we highlight similarities and differences in cognitively intact PD and healthy individuals' response to this intervention. Finally, we believe that our results pave the way for other studies to explore further the relationship between motor and cognitive skills and specify how exercise-dependent plasticity manifests itself following chronic or acute bouts of aerobic activities. As a result, our findings have direct clinical implications for the rehabilitation of PD individuals, by showing that non-pharmacological interventions based on physical exercise can be implemented to improve functioning of individuals with this debilitating disease.

ACKNOWLEDGMENTS

1. This work was supported by the Fonds de Recherche Santé Québec under Grant 26409.

2. The authors wish to thank Dr. Juan Manuel Villalpando and Dr. Thien Tuong Minh Vu who kindly accepted to supervise physical assessment during testing.

References:

Ahlskog, J. E. (2011). Does vigorous exercise have a neuroprotective effect in Parkinson disease? [Review]. *Neurology, 77*(3), 288-294. doi: 10.1212/WNL.0b013e318225ab66

Amano, S., Roemmich, R. T., Skinner, J. W., & Hass, C. J. (2013). Ambulation and Parkinson disease. [Review]. *Phys Med Rehabil Clin N Am, 24*(2), 371-392. doi: 10.1016/j.pmr.2012.11.003

American College of Sport Medicine. (2006). *ACSM's Guidelines for exercise testing and prescription sixth edition*. USA, Philadelphia: Lippincott Williams & Wilkins, Lea & Febiger.

Audiffren, M., André, N., & Albinet, C. (2011). Effets positifs de l'exercice physique chronique sur les fonctions cognitives des seniors: bilan et perspectives. *Revue de neuropsychologie neurosciences cognitives et cliniques, 3*(4), 207-225. doi: 10.3917/rne.034.0207

Bartholomew, J., Ciccolo, J., Spirduso, W., Poon, L., & Chodzo-Zajko, W. (2008). *Exercise, depression, and cognition," in Exercise and Its Mediating Effects on Cognition*.

Beaudreau, S. A., & O'Hara, R. (2009). The Association of Anxiety and Depressive Symptoms with Cognitive Performance in Community-Dwelling Older Adults. *Psychology and Aging, 24*(2), 507-512. doi: 10.1037/a0016035

Beck, A. T., & Beamesderfer, A. (1974). Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry, 7*(0), 151-169. doi: http://www.ncbi.nlm.nih.gov/pubmed/4412100

Bherer, L., Erickson, K. I., & Liu-Ambrose, T. (2013). A Review of the Effects of Physical Activity and Exercise on Cognitive and Brain Functions in Older Adults. [Review]. *J Aging Res, 2013*, 657508. doi: 10.1155/2013/657508

Borg, G. (1982). Psychophysical bases of perceived exertion. *Med Sci Sports Exerc. , 14*, 377–381. doi: http://www.ncbi.nlm.nih.gov/pubmed/7154893

Clark, G., Lum, J., & Ullman, M. (2014). A meta-analysis and meta-regression of serial reaction time tast performance in Parkinson's disease. *Neuropsychology*. doi: 10.1037/neu0000121

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E., & Kramer, A. F. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci, 58*(2), 176-180. doi: 10.1093/gerona/58.2.M176

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., . . . Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A, 101*(9), 3316-3321. doi: 10.1073/pnas.0400266101

Cruise, K. E., Bucks, R. S., Loftus, A. M., Newton, R. U., Pegoraro, R., & Thomas, M. G. (2011). Exercise and Parkinson's: benefits for cognition and quality of life. *Acta Neurol Scand, 123*(1), 13-19. doi: 10.1111/j.1600-0404.2010.01338.x

Curran, T. (1997). Higher-order associative learning in amnesia: Evidence from the serial reaction time task. *Journal of Cognitive Neuroscience, 9*(522-533). doi: 10.1162/jocn.1997.9.4.522

Destrebecqz, A., & Cleeremans, A. (2001). Can sequence learning be implicit? New evidence with the process dissociation procedure. *Psychon Bull Rev, 8*(2), 343-350. doi: 10.1162/jocn.1997.9.4.522

Dirnberger, G., & Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: a review. *J Neuropsychol, 7*(2), 193-224. doi: 10.1111/jnp.12028

Doyon, J. (2008). Motor sequence learning and movement disorders. *Current Opinion in Neurology, 21*(4), 478. doi: 10.1097/WCO.0b013e328304b6a3

Doyon, J., Bellec, P., Amsel, R., Penhune, V., Monchi, O., Carrier, J., . . . Benali, H. (2009). Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav Brain Res, 199*(1), 61-75. doi: 10.1016/j.bbr.2008.11.012

Doyon, J., & Benali, H. (2005). Reorganization and plasticity in the adult brain during learning of motor skills. [Review]. *Curr Opin Neurobiol, 15*(2), 161-167. doi: 10.1016/j.conb.2005.03.004

Ellis, T., Cavanaugh, J. T., Earhart, G. M., Ford, M. P., Foreman, K. B., Fredman, L., . . . Dibble, L. E. (2011). Factors Associated With Exercise Behavior in People With Parkinson Disease. *Physical Therapy, 91*(12), 1838-1848. doi: 10.2522/ptj.20100390

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A, 108*(7), 3017-3022. doi: 10.1073/pnas.1015950108

Fama, R., & Sullivan, E. V. (2002). Motor sequencing in Parkinson's disease: relationship to executive function and motor rigidity. *Cortex, 38*(5), 753-767. doi: 10.1016/S0010-9452(08)70042-X

Folstein, M., Folstein, S., & McHugh, P. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician *J Psychiatr Res* (Vol. 12, pp. 189 - 198).

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., . . . LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders, 23*(15), 2129-2170. doi: 10.1002/mds.22340

Goodwin, V. A., Richards, S. H., Taylor, R. S., Taylor, A. H., & Campbell, J. L. (2008). The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov Disord, 23*(5), 631-640. doi: 10.1002/mds.21922

Gracies, J. M. (2010). [Neurorehabilitation in parkinsonian syndromes]. *Rev Neurol (Paris), 166*(2), 196-212. doi: 10.1016/j.neurol.2009.10.026

Herman, T., Giladi, N., Gruendlinger, L., & Hausdorff, J. M. (2007). Six weeks of intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil, 88*(9), 1154-1158. doi: 10.1016/j.apmr.2007.05.015

Herman, T., Giladi, N., & Hausdorff, J. M. (2009). Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review. *J Neural Transm, 116*(3), 307-318. doi: 10.1007/s00702-008-0139-z

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology, 17*(5), 427-442. doi: http://www.ncbi.nlm.nih.gov/pubmed/6067254

Jackson, A. S., Blair, S. N., Mahar, M. T., L.T., W., Ross, R. M., & Stuteville, J. E. (1990). Prediction of functional aerobic capacity without exercise testing. *Medicine & Science in Sports & Exercise, 22*(6), 863-870. doi: http://www.ncbi.nlm.nih.gov/pubmed/2287267

Jellinger, K. A. (2012). Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. [Review]. *Mov Disord, 27*(1), 8-30. doi: 10.1002/mds.23795

Johnco, C., Wuthrich, V. M., & Rapee, R. M. (2015). THE IMPACT OF LATE-LIFE ANXIETY AND DEPRESSION ON COGNITIVE FLEXIBILITY AND COGNITIVE RESTRUCTURING SKILL ACQUISITION. *Depression and Anxiety*, n/a-n/a. doi: 10.1002/da.22375

Kudlicka, A., Clare, L., & Hindle, J. V. (2011). Executive functions in Parkinson's disease: Systematic review and meta-analysis. *Movement Disorders, 26*(13), 2305-2315. doi: 10.1002/mds.23868

Langlois, F., Vu, T. T., Chasse, K., Dupuis, G., Kergoat, M. J., & Bherer, L. (2013). Benefits of physical exercise training on cognition and quality of life in frail older adults. *J Gerontol B Psychol Sci Soc Sci, 68*(3), 400-404. doi: 10.1093/geronb/gbs069

Liu-Ambrose, T., Nagamatsu, L. S., Graf, P., Beattie, B. L., Ashe, M. C., & Handy, T. C. (2010). Resistance training and executive functions: a 12-month randomized controlled trial. [Randomized Controlled Trial]. *Arch Intern Med, 170*(2), 170-178. doi: 10.1001/archinternmed.2009.494

Mailey, E. L., White, S. M., Wojcicki, T. R., Szabo, A. N., Kramer, A. F., & McAuley, E. (2010). Construct validation of a non-exercise measure of cardiorespiratory fitness in older adults. *BMC Public Health, 10*, 59. doi: 10.1186/1471-2458-10-59

Marinus, J., Verbaan, D., & van Hilten, J. J. (2011). The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology, 76*(22), 1944; author reply 1944-1945. doi: 10.1212/WNL.0b013e318219dc77

McAuley, E., Elavsky, S., Spirduso, W., Poon, L., & Chodzo-Zajko, W. (2008). *Exercise, depression, and cognition," in Exercise and Its Mediating Effects on Cognition*.

McAuley, E., Szabo, A. N., Mailey, E. L., Erickson, K. I., Voss, M., White, S. M., . . . Kramer, A. F. (2011). Non-Exercise Estimated Cardiorespiratory Fitness: Associations with Brain Structure, Cognition, and Memory Complaints in Older Adults. *Ment Health Phys Act, 4*(1), 5-11. doi: 10.1016/j.mhpa.2011.01.001

McKee, K. E., & Hackney, M. E. (2013). The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease. *J Mot Behav, 45*(6), 519-529. doi: 10.1080/00222895.2013.834288

Murray, D. K., Sacheli, M. A., Eng, J. J., & Stoessl, A. J. (2014). The effects of exercise on cognition in Parkinson's disease: a systematic review. *Transl Neurodegener, 3*(1), 2047-9158. doi: 10.1186/2047-9158-3-5

Nadeau, A., Pourcher, E., & Corbeil, P. (2014). Effects of 24 wk of Treadmill Training on Gait Performance in Parkinson's Disease. *Medicine & Science in Sports & Exercise, 46*(4), 645-655 doi: 10.1249/MSS.0000000000000144

Nissen, M. J., & Bullemer, P. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology, 19*(1), 1-32. doi: http://dx.doi.org/10.1016/0010-0285(87)90002-8

Osman, A., Kopper, B. A., Barrios, F. X., Osman, J. R., & Wade, T. (1997). The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. *J Clin Psychol, 53*(1), 7-14. doi: 10.1002/(SICI)1097-4679(199701)53:1<7::AID-JCLP2>3.0.CO;2-S

Petzinger, G. M., Fisher, B. E., McEwen, S., Beeler, J. A., Walsh, J. P., & Jakowec, M. W. (2013). Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *The Lancet Neurology, 12*(7), 716-726. doi: http://dx.doi.org/10.1016/S1474-4422(13)70123-6

Petzinger, G. M., Fisher, B. E., Van Leeuwen, J. E., Vukovic, M., Akopian, G., Meshul, C. K., . . . Jakowec, M. W. (2010). Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. *Mov Disord, 25 Suppl 1*, S141-145. doi: 10.1002/mds.22782

Physiology, C. S. f. E. (1996). *Professional Fitness Lifestyle Consultant 2. Reference Manual*. Ottawa.

Predovan, D., Fraser, S. A., Renaud, M., & Bherer, L. (2012). The effect of three months of aerobic training on stroop performance in older adults. *J Aging Res, 2012*, 269815. doi: 10.1155/2012/269815

Ridgel, A. L., Kim, C. H., Fickes, E. J., Muller, M. D., & Alberts, J. L. (2011). Changes in executive function after acute bouts of passive cycling in Parkinson's disease. [Research Support, Non-U.S. Gov't]. *J Aging Phys Act, 19*(2), 87-98. doi: http://www.ncbi.nlm.nih.gov/pubmed/21558565

Ridgel, A. L., Vitek, J. L., & Alberts, J. L. (2009). Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil Neural Repair, 23*(6), 600-608. doi: 10.1177/1545968308328726

Sarazin, M., Deweer, B., Merkl, A., Von Poser, N., Pillon, B., & Dubois, B. (2002). Procedural learning and striatofrontal dysfunction in Parkinson's disease. *Mov Disord, 17*(2), 265-273. doi: 10.1002/mds.10018/asset/10018_ftp.pdf?v=1&t=i4jwhi82&s=988887c2b17dac566474b141b6693293a23942da

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., . . . Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med, 72*(3), 239-252. doi: 10.1097/PSY.0b013e3181d14633

Speelman, A. D., van de Warrenburg, B. P., van Nimwegen, M., Petzinger, G. M., Munneke, M., & Bloem, B. R. (2011). How might physical activity benefit patients with Parkinson disease? [10.1038/nrneurol.2011.107]. *Nat Rev Neurol, 7*(9), 528-534. doi: 10.1038/nrneurol.2011.107

Spirduso, W., Francis, K., & MacRae, P. (2005). *Physical Dimensions of Aging*: Human Kinetics, Ill, USA.

Spreen, O. S., Esther; Elisabeth M. S. Sherman (2006). *A compendium of neuropsychological tests: administration, norms, and commentary*.

Stefanova, E. D., Kostic, V. S., Ziropadja, L., Markovic, M., & Ocic, G. G. (2000). Visuomotor skill learning on serial reaction time task in patients with early Parkinson's disease. *Mov Disord, 15*(6), 1095-1103. doi: http://www.ncbi.nlm.nih.gov/pubmed/11104191

Tanaka, K., Quadros, A. C., Jr., Santos, R. F., Stella, F., Gobbi, L. T., & Gobbi, S. (2009). Benefits of physical exercise on executive functions in older people with Parkinson's disease. [Controlled Clinical Trial]. *Brain Cogn, 69*(2), 435-441. doi: 10.1016/j.bandc.2008.09.008

Uc, E. Y., Doerschug, K. C., Magnotta, V., Dawson, J. D., Thomsen, T. R., Kline, J. N., . . . Darling, W. G. (2014). Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting. *Neurology, 83*(5), 413-425. doi: 10.1212/WNL.0000000000000644

Verstynen, T. D., Lynch, B., Miller, D. L., Voss, M. W., Prakash, R. S., Chaddock, L., . . . Erickson, K. I. (2012). Caudate Nucleus Volume Mediates the Link between Cardiorespiratory Fitness and Cognitive Flexibility in Older Adults. *J Aging Res, 2012*, 939285. doi: 10.1155/2012/939285

Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T., & Kramer, A. F. (2011). Exercise, brain, and cognition across the life span. *J Appl Physiol, 111*(5), 1505-1513. doi: 10.1152/japplphysiol.00210.2011

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., . . . Kramer, A. F. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci, 2*. doi: 10.3389/fnagi.2010.00032

Table 1. Article 1: Demographics of the two groups of participants

Variables [a]	HC (n=20)	PD (n=19)	p-value
Sex (male\female)	8\12	13\6	0,07[b]
Age (years)	64 (8.19)	59 (7.11)	0.06[c]
Education	15.7 (2.36)	15.05 (2.78)	0.43[c]
Physical activity [d]	2.1 (1.17)	1.84 (1.26)	0.51[c]
Cognition (MMSE\MOCA) [e]	29.18\28.56 (1.25\1.51)	28.4\27.21 (1.34\1.85)	0.275\0.08[c]
Depression [f]	4.8 (4.5)	10.5 (8.3)	*0.01[c]
Anxiety [f]	2.1 (2.7)	8.6 (8.4)	*0.002[c]
Hoehn & Yahr score	N\A	2 (0)	N\A
UPDRS total score	N\A	21.84 (6.16)	N\A
Years diagnosed	N\A	8.1 (9.12)	N\A

[a] Values represent mean (standard deviation), except for 'Sex', where values represent counts.

[b] *p*-value from chi-square test

[c] *p*-value from ANOVA

[d] Jackson's questionnaire assessing activity level at baseline

[e] 5 PD and 11 HC were assessed with MMSE and 14 PD and 9 HC with MOCA

[f] Beck depression inventory and Beck anxiety were used

Table 2. Article 1: Group average on physical and cognitive assessments before and after aerobic exercise training for the two groups of participants

Physical Variables	**HC Pre**	**HC Post**	**p-value** [b]	**PD Pre**	**PD Post**	**p-value** [b]
Estimated VO_2max (mL/kg/min)	28.1 (5.7)	31.6 (7.6)	*0.001	24.8 (6.7)	27.7 (7.4)	*0.003
Estimated maximal aerobic power (Watts)	138.6 (45.2)	160.1 (50)	*0.001	130.3 (53.4)	148 (57.4)	*0.003
Systolic blood pressure (mm Hg)	137.3 (18.3)	123 (14)	*0.001	127.6 (13.1)	120.4 (11.7)	0.072
Diastolic blood pressure (mm Hg)	80.5 (9.6)	76.5 (6.9)	0.093	77.9 (10.3)	75 (7.6)	0.214
Heart rate at rest (BPM)	68.9 (11.3)	63.8 (8.3)	0.09	70.4 (11.9)	66.2 (8.4)	*0.039
Weight (kg)	72 (13)	71.3 (13.2)	*0.024	79.9 (18.6)	79.3 (18.6)	0.281
Cognitive Variables	**HC Pre**	**HC Post**	**p-value**[b]	**PD Pre**	**PD Post**	**p-value**[b]
Stroop inhibition (s)	115.4 (21)	106.4 (25.2)	*0.025	128.5 (29.3)	118.8 (26)	*0.008
Trail flexibility (s)	75 (28.6)	70 (33)	0.210	85.5 (47.7)	75.7 (29.4)	0.396

[a] Values are mean (standard deviation)

[b] p-value from analysis of variance.

* indicate statistically significant differences adjusted for multiple comparisons (multivariate tests)

Figure 1. A. Article 1: Diagram illustrating the experimental procedure. Figure 1. B. Diagram illustrating the motor sequence learning task

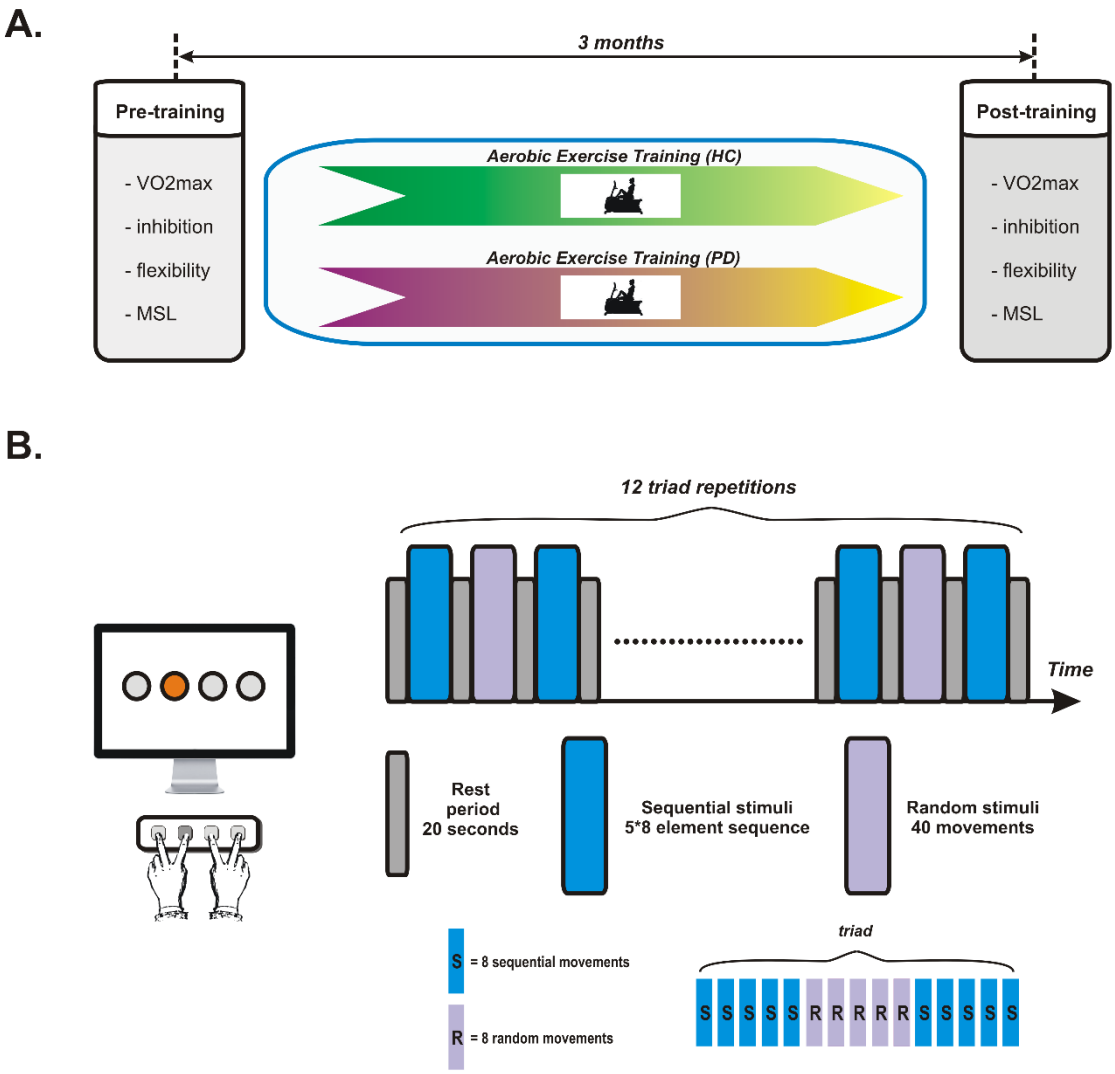
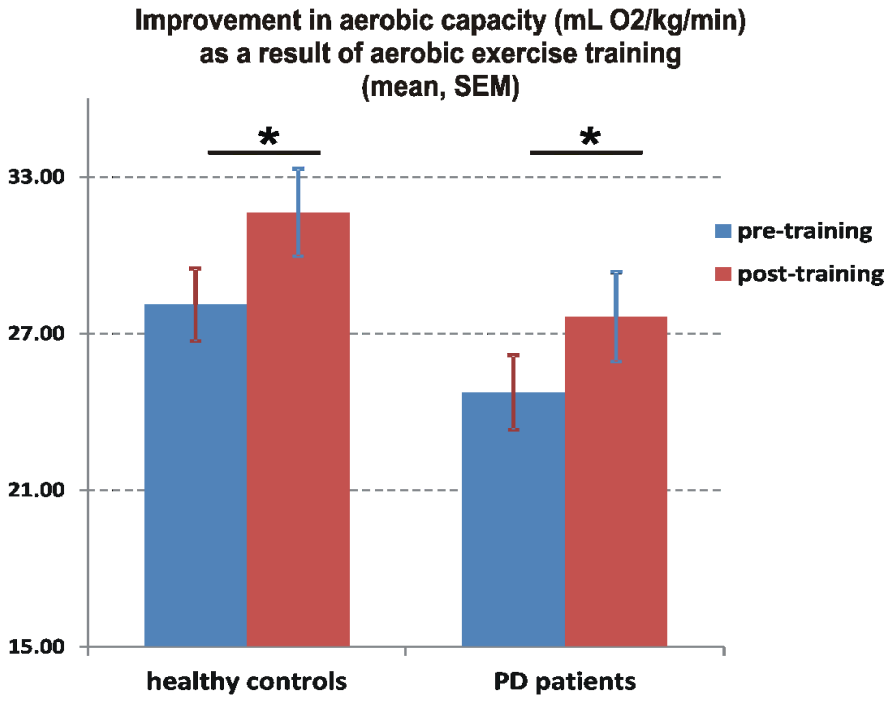


Figure 1. A. Diagram illustrating the experimental procedure. Participants were assessed before and after 3 months of aerobic exercise training. **B.** Diagram illustrating the motor sequence learning task. Blocks of 40 stimuli were presented in triads alternating between random (R) and sequential (S) movements. Procedural learning was assessed by the difference in reaction time between R and S blocks.

Figure 2. A. Article 1: Aerobic capacity before and after 3 months of training. Figure 2. B. Magnitude of Stroop interference effect before and after aerobic exercise training

A.



B.

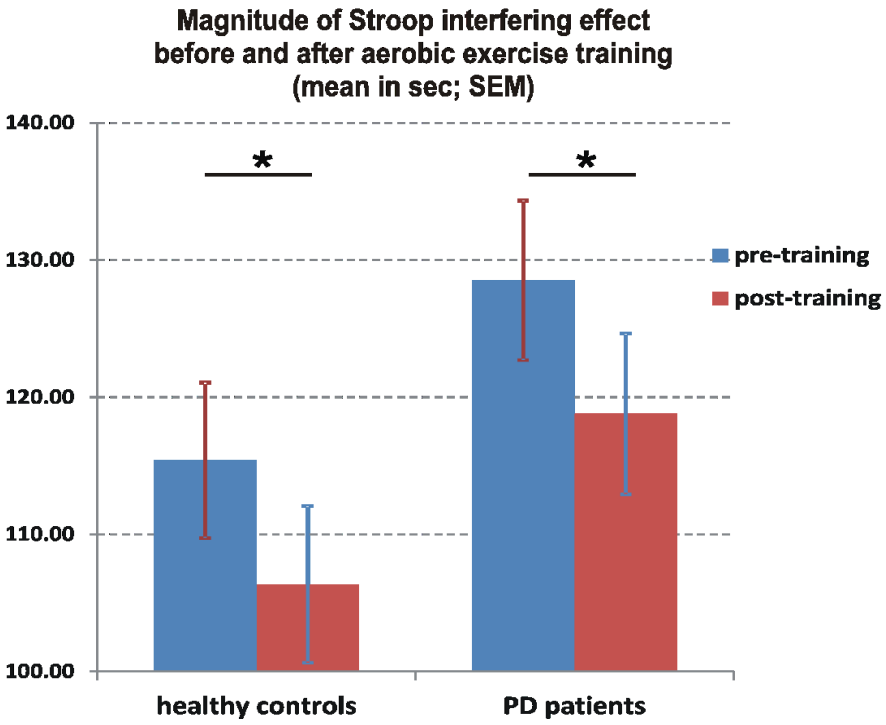


Figure 2. A. Aerobic capacity (ml O_2 / kg / min) before and after 3 months of aerobic exercise training for PD patients and healthy controls (group average, standard error of the mean). Stars indicate statistically significant differences pre- to post- training ($p<0.05$ corrected for multiple comparisons). **B.** Magnitude of Stroop interference effect (seconds) before and after 3 months of aerobic exercise training for PD patients and healthy controls (group average, standard error of the mean). Stars indicate statistically significant differences pre- to post-training ($p<0.05$ corrected for multiple comparisons).

Figure 3. Article 1: Magnitude of motor sequence learning effect before and after aerobic exercise training

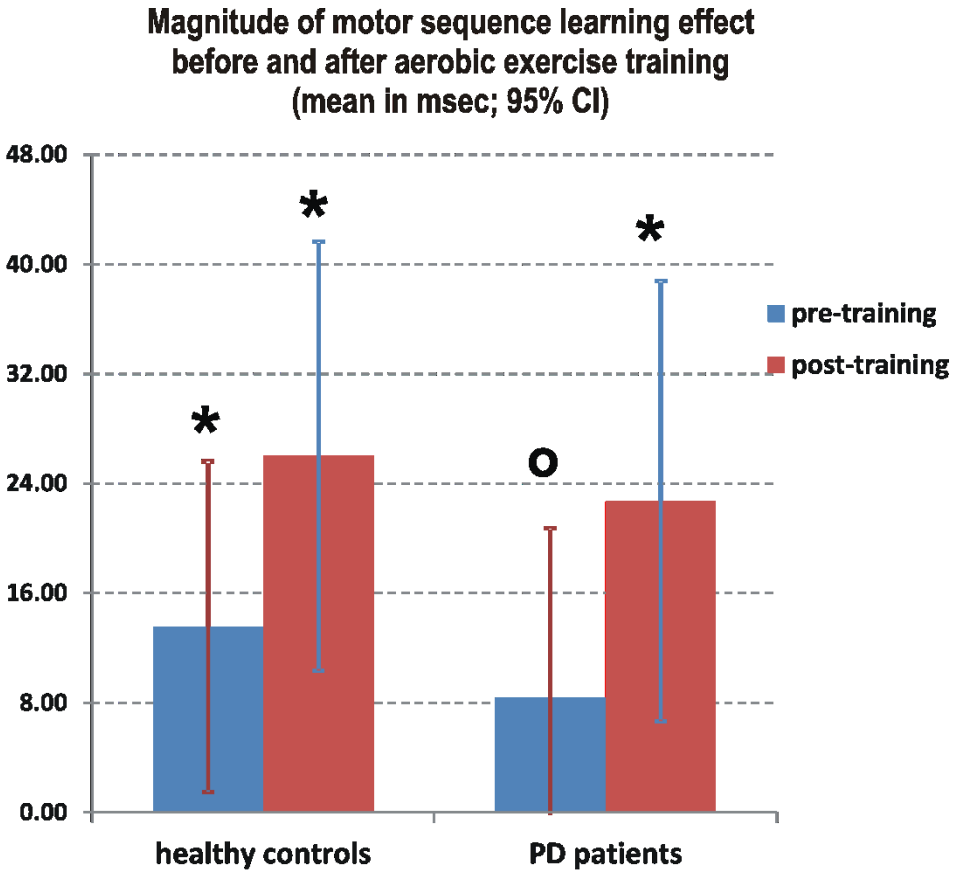


Figure 3. Magnitude of the sequence learning effect (difference between random and sequential blocks, in milliseconds) before and after 3 months of aerobic exercise training for PD patients and healthy controls (group average, 95% CI). Stars indicate statistically significant sequence learning effects greater than zero ($p<0.05$ corrected for multiple comparisons). The circle indicates a learning effect that was not different than zero.

Article 2: Influence of Aerobic Exercise Training on the Neural Correlates of Motor Learning in Parkinson's Disease Individuals

Submitted to Neuroimage Clinical

Statement of contribution for all authors:

Catherine Duchesne: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision

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Influence of Aerobic Exercise Training on the Neural Correlates of Motor Learning in Parkinson's Disease Individuals

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Abstract

Background: Aerobic exercise training (AET) has been shown to provide general health benefits, and to improve motor behaviours in particular, in individuals with Parkinson's disease (PD). However, the influence of AET on motor learning capacity in PD, as well as the change in neural substrates mediating this effect remains to be explored. Objective: In the current study, we employed functional Magnetic Resonance Imaging (fMRI) to assess the effect of a 3-month AET program on the neural correlates of implicit motor sequence learning (MSL). Methods: 20 healthy controls (HC) and 19 early PD individuals participated in a supervised, high-intensity, stationary recumbent bike training program (3 times/week for 12 weeks). Exercise prescription started at 20 minutes (+5 minutes/week up to 40 minutes) based on participant's maximal aerobic power. Before and after the AET program, participants' brain was scanned while

performing an implicit version of the Serial Reaction Time Task. Results: Brain imaging data revealed pre-post MSL-related increases in functional activity in the hippocampus, striatum and cerebellum in PD patients as compared to controls. Importantly, the functional brain changes in PD individuals correlated with changes in aerobic fitness: a positive relationship was found with increased activity in the hippocampus and striatum, while a negative relationship was observed with the cerebellar activity. Conclusion: Our results reveal, for the first time, that exercise training produces functional changes in known motor learning related brain structures that are consistent with improved behavioural performance observed in PD patients. These results suggest that, AET can be a valuable non-pharmacological intervention to promote, not only physical fitness in early PD, but also better motor learning capacity useful in day-to-day activities through increased plasticity in motor related structures. Key words: Parkinson's disease, exercise, motor learning, fMRI

AET: Aerobic exercise training, PD: Parkinson's disease, MSL: Motor sequence learning, HC: Healthy control

Influence of Aerobic Exercise Training on the Neural Correlates of Motor Learning in Parkinson's Disease Individuals

1. INTRODUCTION

Parkinson's disease (PD) is a progressive disorder of multifactorial etiology characterized by motor symptoms such as tremor, rigidity, bradykinesia and gait difficulties. Motor deficits in PD are due to an abnormal neuronal activity of the motor circuit in the basal ganglia, predominantly involving the striatum and the putamen (Amano et al., 2013). Such

brain dysfunctions lead to motor functional difficulties, including impairments in learning new motor skills (Clark, 2014), hence adding burden to day-to-day activities and leading sometimes to inactivity and exacerbation of disease manifestation (van Nimwegen et al., 2011). As a result, both the known striatal pathology in PD and the lack of physical activity imposed by the disease can jeopardize the patients' capacity to acquire new motor skilled behaviours throughout the progression of the neurodegenerative process.

Apart from the treatments commonly used to manage PD symptoms (e.g., dopaminergic-derived drug treatments and DBS), alternative treatments, such as physical activity, have recently been investigated in PD. Such a new approach is based on an increasing number of studies in animals and humans, which indicate that physical exercise may attenuate symptoms of the disease, and even exert a neuroprotective effect (Hirsch et Farley, 2009b). In rodents for example, mice model of PD forced to exercise on a treadmill did not develop behavioural deficits and significantly preserved nigrostriatal neuronal connections as well as striatal dopamine levels compared to sedentary mice (Pothakos et al., 2009; Yoon et al., 2007). Petzinger et al. (2007) have also found that a similar exercise intervention improves efficiency of brain dopamine cells more in mice who exercised as compared to those that did not. Altogether, these results suggest that exercise improves dopaminergic neurotransmission efficiency by modifying the areas of the brain (e.g., the substantia nigra and basal ganglia) where dopamine signals originate (Petzinger et al., 2007). Given that movement is modulated through dopamine, findings in rodents suggest a possible interaction between behaviour and neuronal cerebral viability in the striatum after cardiovascular exercise (Petzinger et al., 2010).

In humans, studies in PD individuals have demonstrated significant improvement in gait and mobility following supervised physical exercise (Beall et al., 2013; Herman et al., 2007; Nadeau et al., 2014; Ridgel et al., 2011; Ridgel et al., 2009; van Eijkeren et al., 2008). Among the many different types of physical training programs (e.g., resistance training, flexibility, coordination, etc.), aerobic exercise training (AET) has been the most studied so far, and the one that has shown the most unequivocal benefits on health across the life span (Voss et al., 2011). Although the underlying mechanisms in PD still remain conjectural, it has been hypothesized that exercise-dependent plasticity following AET acts on the brain in a similar manner as the dopaminergic-derived treatments, using the same pathways to produce symptomatic relief (Beall et al., 2013). It is thus possible that exercise dependent change can have beneficial effects on motor skill learning processes. More specifically, AET may restore motor sequence learning (MSL), a capacity that is frequently impaired in PD (Gillian M. Clark, 2014), by improving brain functioning at the level of the striatum or motor-related associated circuits.

Despite behavioural impairment observed when performing MSL tasks, studies have demonstrated that similar motor-related brain regions seem to be recruted in individuals with PD (Carbon, Reetz, Ghilardi, Dhawan et Eidelberg, 2010; Schendan, Tinaz, Maher et Stern, 2013; Werheid, Zysset, Müller, Reuter et von Cramon, 2003) as in healthy aging controls (Albouy et al., 2015; Doyon, Penhune et Ungerleider, 2003). Specifically, functional brain imaging studies with healthy participants have shown that brain plasticity associated with MSL relies on recruitment of striatum and hippocampus, as well as the cerebellum, motor cortical regions, and prefrontal and parietal cortex (Albouy et al., 2015; Doyon et al., 2009). Studies

with PD individuals yielded similar regions, but different patterns of interaction between them, in the cortico-striatal and medio-temporal lobe networks (Carbon et al., 2010; Schendan et al., 2013; Werheid, Zysset, Müller, et al., 2003). Furthermore, these findings could be influenced by the disease stage and the impact of dopaminergic medication (see Ruitenberg et al., 2015 for a review). However, studies directly comparing the neuronal substrate involved in MSL in healthy and PD are few and those directly comparing the effects of aerobic exercise on the MSL neuronal substrate in healthy and PD are non-existent. In fact, one study demonstrated that a single bout of high-intensity aerobic exercise facilitates motor sequence learning in healthy individuals (Mang, Snow, Campbell, Ross et Boyd, 2014), but the neural correlates of these effects have never been investigated at the whole brain level; and furthermore, they have never been specific to the chronic effects of exercise.

Thus, to date, there is a lack of evidence regarding the effects of aerobic training exercise on the MSL functional neuronal substrate in both healthy and PD. In response to this knowledge gap, the principal aim of the present study was to investigate, with whole brain functional magnetic resonance imaging (fMRI), the neural substrate mediating the effects of cardiorespiratory exercise on MSL in both PD and healthy control (HC) individuals. We have already presented behavioral evidence that 3-month AET improved MSL capacity in both healthy and PD individuals, as well as executive functions in PD (Duchesne et al., 2015). In the current article, we present the neuroimaging data related to MSL from the same study and we hypothesize that 1) AET will improve MSL capacity through augmented activity in the cortico-striatal (CS) system in PD, and 2) MSL-related cerebral activity changes observed after AET will be linked to improvement in aerobic fitness in both PD and HC groups.

2. METHODS

2.1. *Participants*

A total of 39 participants (18 women) aged between 40-80 years old participated in the present study; 19 were diagnosed with PD and 20 were healthy control (HC) subjects. To control for pre-existing experience in tasks requiring highly coordinated finger dexterities, PD and HC subjects had to have no previous training in playing a musical instrument, nor any training as a professional typist. Other exclusion criteria included the presence of other neurological disorders, comorbidities likely to affect gait, or any history of smoking or heart diseases, and high baseline physical activity.

These two groups were well matched with respect to their sex distribution, age, number of years of education and fitness level (as there were no significant differences on any of these variables prior to the AET intervention program, see Table 1). Yet, and as expected, significant group differences were found on Beck's depression and anxiety scales, with PD patients showing higher scores on both scales as compared with HC participants.

2.2. Clinical assessment of health and cardiovascular fitness

First, PD subjects were recruited based on a neurological assessment performed by an expert neurologist. Clinical assessments of the participants' health and physical activity level were then performed by a geriatrist, neuropsychologist and physiologist using the following tests: the United Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2008), the Montreal Cognitive Assessment (MOCA) or Mini Mental State Evaluation (MMSE) (Nazem et al., 2009),

the Beck Depression Inventory (BDI) (Beck et Beamesderfer, 1974) and Beck Anxiety Inventory (BAI) (Osman et al., 1997), as well as the Jackson's Questionnaire (Jackson et al., 1990).

Participants' cardiovascular fitness level was evaluated using either a submaximal aerobic test (11 HC, 5 PD) or a medically supervised maximal oxygen uptake test (9 HC, 14PD). The protocol required a five minutes resting period before measuring heart rate, blood pressure, and aerobic capacity. For the evaluated with a sub-maximal test (using a recumbent bike), the test started with a workload stage of 35 or 50 Watts (W) (for women and men, respectively), lasting one minute; the intensity increasing progressively by 15W every minute until they reached 85% of their predicted maximal heart rate (HRmax = 208-0.7*age). When the target heart rate was reached, participants were asked to complete the current stage (if possible). The power level (in W) of the last completed stage was used to extrapolate the maximal aerobic power (MAP). Then, VO_2max estimation was calculated with body weight (kg) and MAP (W) measures, using the American College Sport Medicine's formula: VO_2=(10,8*Watts/weight)+7 (Marsh, 2012); MAP estimation was used for exercise prescription. For the participants that were evaluated with a graded cycling (one minute workload stage) maximal test, the protocol started again at 35W or 50W (for women and men, respectively), and the intensity progressively increased by 15W every minute until maximal efforts criteria were fulfilled (e.g., age predicted maximal heart rate +/- 10 bpm and VO_2 plateau), or until subjects could not maintain the required workload anymore (fatigue). Aerobic capacity (VO_2max) was measured directly using a breath-by-breath system. The last completed stage power (W) was recorded and used for exercise prescription (American College of Sport Medicine, 2006) . Importantly, PD individuals performed the stress test while following

their usual medication regimen, which did not change during the study period. In addition, for each patient, the stress tests were administered at the same time of day and did not change pre-to-post AET.

2.3. Motor sequence learning task

Subjects' implicit MSL capacity was evaluated using a version of the serial reaction time (SRT) task (Nissen et Bullemer, 1987a), in which participants were asked to press buttons on a keyboard in response to corresponding visual stimuli presented on a screen. Unbeknown to the participants, stimuli were presented in a random or in a repeating sequential order, in blocks of 40 stimuli each. These blocks were presented in triplets (Sequence, Random, Sequence), with a total of 12 triplets during the entire training session. For the sequential blocks, two 8-item, second order conditional sequences (2-4-3-1-4-2-1-3 and 3-1-2-4-1-3-4-2) were used and counterbalanced between sessions (pre-, post-AET) and subjects, in order to avoid repetition of the learned sequence for the same individual. For each trial, reaction time (i.e., the time between the onset of the stimulus to the completion of the response. To assess sequence learning, reaction times (RTs) and accuracy were compared between the sequence and random blocks, with faster RTs and better accuracy for sequence as compared to the random blocks reflecting greater motor sequence learning capacity. More information on motor task procedure can be found in previous paper (Duchesne et al., 2015).

2.4. Behavioural statistical data analysis

The main independent variables included in our analyses were the presence/absence of the disease (i.e., PD vs. HC groups, between group variable) and the effect of aerobic training, expressed as the time of testing (pre- vs. post- intervention, within-group variable).

Dependent variables included the following: physical fitness (expressed as VO2max estimate) and the subject's performance (learning score) on the MSL task. We first assessed the relationship between independent and dependent variables using a mixed repeated measures analysis of variance (ANOVA), with group as between-subjects factor and time of testing as within-subjects factor. In order to account for the effect of multiple comparisons, the statistical significance was adjusted using the Bonferroni method. The two psychological variables (depression and anxiety) were used as covariates in all subsequent analyses involving behavioral data, to control for group differences at baseline on these variables. All analyses were performed with SPSS 20 (IBM Inc, Armonk, NY).

2.5. Experimental procedure

Participants were tested on two time points: pre and post training. Each occasion was similar and included two different days of testing that occurred at least 48 hours apart. On day 1, participants were first informed in details about the study protocol before signing a consent form, which was approved by the "Regroupement Neuroimagerie Québec" Ethics Review Committee. Participants were then evaluated with respect to their functional capacities and cardiorespiratory fitness level, as well as to their medical and psychological status. This was followed by giving instructions to participants regarding the scanning procedure and the motor sequence learning task while lying in a mock scanner. During this familiarization session, participants had the time to practice a randomly assigned trial the correct positioning of the fingers on the response box. On Day 2, participants' brain was then scanned while completing the motor sequence task while positioned in the magnetic resonance imaging system available

at the “Unité de Neuroimagerie Fonctionnelle” from the “Université de Montréal”, the latter session occurring before and after the AET program.

2.5.1. The exercise protocol procedure

The cardiorespiratory fitness program involved three months of recumbent bike-training, three times a week, 1 hour/session, which occurred at the same time of day. The exercise intensity prescription was based on the subject’s maximal aerobic power output from the maximum volume of oxygen (VO_2peak) uptake conducted on pre-test day (American College of Sport Medicine, 2006; Physiology, 1996). Duration of the exercise program started at 20 minutes and 60% of intensity per session, and was then increased by steps of 5 minutes and 5% of intensity every week until participants reached 40 minutes of training at 80% intensity. To reach a high-intensity level, bike speed was maintained at 60 revolutions per minute (RPM). As such, to achieve the desired bike resistance power and adjust intensity level (if needed), the work intensity was based on power output (Watt), controlling for subject’s heart rate. In addition, rate of perceived exertion (Borg scale) (Borg, 1982) was assessed on each training session. The target of 75% or more in participation rate in the fitness training program was achieved. In addition, PD individuals did not change their medication regimen for the entire duration of the study.

2.6. fMRI data acquisition and analysis

Functional MRI-series were acquired using a 3.0T TIM TRIO scanner system (Siemens, Erlangen, Germany), equipped with a 12-channel head coil. Multislice T2*-weighted fMRI images were obtained with a gradient echo-planar sequence using axial slice orientation in an ascending order (TR = 2650 ms, TE = 30 ms, FA = 90°, 43 transverse slices, 3 mm slice thickness,

10% inter-slice gap, FoV = 220×220 mm^2, matrix size = 64×64×43, voxel size = 3.4×3.4×3 mm^3). A structural T1-weigthed 3D MP-RAGE sequence (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, FA = 9°, 176 slices, FoV = 256×256 mm^2, matrix size = 256×256×176, voxel size = 1×1×1 mm^3) was also acquired in all subjects. Head movements were minimized using cushions and instructions prior to scanning.

Functional volumes were pre-processed and analysed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/; Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB. Functional scans of each session were realigned using rigid body transformations, iteratively optimized to minimize the residual sum of squares between the first and each subsequent image separately for each session, hence creating a mean realigned image. The mean functional image was then coregistered to the structural T1-image using a rigid body transformation optimized to maximize the normalized mutual information between the two images. Coregistration parameters were then applied to the realigned BOLD time series. An average subject-based template was created using DARTEL in SPM8, and registered to MNI space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca). All functional and anatomical images were then normalized using the resulting template. Finally, all functional images were spatially smoothed using an isotropic 8-mm full-width at half-maximum (FWHM) Gaussian kernel.

The analysis of fMRI data, based on a summary statistics approach, was conducted in 2 serial steps, accounting respectively for fixed and random effects. For each subject, changes in brain regional responses were estimated through a model including responses to the sequence and random conditions separately in each practice session (pre and post). These four

regressors consisted of boxcars convolved with the canonical hemodynamic response function. Instructions as well as movement parameters derived from realignment of the functional volumes were also included as covariates of no interest. High-pass filtering was implemented in the design matrix using a cut-off period of 128 seconds to remove slow drifts from the time series. Serial correlations in fMRI signal were estimated using an autoregressive (order 1) plus white noise model and a restricted maximum likelihood (ReML) algorithm.

The contrast of interest explored the main motor sequence learning effect (SEQUENCE - RANDOM) between sessions (POST - PRE). The resulting contrast images of each subject were then further spatially smoothed (Gaussian kernel 6mm FWHM) and entered in a second-level analysis, accounting for inter-subject variance. In the second level analyses, one sample t-tests were performed to explore main motor sequence learning effect between-sessions within each group (HC and PD) separately. Subsequently, two-sample t tests were performed in order to compare this effect between groups (HC vs PD).

Furthermore, we performed an additional analysis in order to assess the relationship between these changes in brain activation and aerobic fitness across sessions. Specifically, the main sequence learning effect between sessions was regressed against changes in aerobic fitness to ascertain whether these effects were related to the AET. As before, one sample t-tests were performed to explore the regression effects within each group (HC and PD) separately, and two-sample t tests were performed in order to compare the regression effects between groups (HC vs PD).

The set of voxel activation values resulting from each analysis described above (activation and regression analyses) were displayed in statistical maps at a threshold of $p <$

0.005 (uncorrected for multiple comparisons). However, all statistical inferences were performed at a threshold of $p < 0.05$ after family-wise error (FWE) correction for multiple comparisons over small spherical volumes (10 mm radius) located in *a priori* defined structures of interest reported in published work on motor learning.

3. RESULTS

3.1. Behavioral results

3.1.1. Aerobic exercise training

The 3-months aerobic training regimen yielded a significant improvement in aerobic fitness as indicated by the estimated VO_2max in the two groups combined ($F_{1,35}$=17.333, p<0.001), as well as in both HC ($F_{1,35}$=15.188, p<0.001) and PD ($F_{1,35}$=9.984, p<0.003) groups separately. Also the estimated power level increased significantly following AET in the two groups combined ($F_{1,35}$=16.461, p<0.001) as well as in the HC ($F_{1,35}$=14.930, p<0.001) and PD ($F_{1,35}$=10.500, p<0.003) groups separately. However, there was no significant group x session interaction, nor any group differences for all of these fitness measures. Altogether, these results indicate that the effect of exercise had similar physiological benefits in both groups of participants who significantly increased their individual level of aerobic fitness (Duchesne et al., 2015).

3.1.2. *Motor sequence learning*

The detailed results of the MSL task for the two conditions (Sequence and Random) and groups (PD and HC), both pre and post training session are reported elsewhere (Duchesne et al., 2015). Even though the interaction between groups and conditions regardless of time of testing (i.e. pre- vs. post-AET) was not significant (F1,35=0,266, p=0.6), across all participants,

we observed a significant difference in reaction time between conditions ($F_{1,35}=17.712$, $p<0.001$), with performance during the sequence being faster than during the random condition; an indicator of motor sequence learning capacity. In addition, there was a marginally significant interaction between condition and session ($F_{1,35}=3.650$, $p=0.064$) across he two groups, hence demonstrating a trend that the participant's motor sequence learning capacity tended to improve more than their performance in the random condition following AET.

Within-group analyses revealed between-session improvement in reaction time for both sequence ($F_{1,35}=12.525$, $p<0.001$) and random conditions ($F_{1,35}=8.422$, $p<0.006$); whereas PD individuals showed AET-related improvement in RT only for the sequential condition ($F_{1,35}=5.173$, $p<0.029$). Most importantly, when assessing motor sequence learning capacity in each group, we identified a significant sequence learning effect (i.e., sequential - random conditions) pre-AET in HC ($F_{1,35}=4.059$, $p=0.052$), but not in PD ($F_{1,35}=1.427$, $p=0.24$). After AET, however, both groups showed significant sequence learning ($F_{1,35}=7.134$, $p<0.011$, for HC and $F_{1,35}=8.878$, $p<0.005$).

3.2. Brain imaging results

3.2.1. Functional brain changes related to motor learning capacity following AET in PD

To investigate the effects of AET on the neural correlates specific to motor sequence learning, we contrasted the main sequence learning effect [Sequence – Random] by session [POST – PRE] within PD group. The results of this analysis revealed significant training-related changes for PD's individuals. Specifically, brain responses reflecting motor sequence learning

capacity increased significantly post-AET in the temporal lobes, left ventral striatum, left hippocampus, cerebellar lobules 8 and 9 bilaterally and right crus (Table 2. Fig. 1).

To test whether pre-post functional brain changes expressing motor learning capacity were indeed related to improvement in aerobic fitness, we conducted a regression analysis between changes in estimated VO_2max and changes in MSL brain responses ([Sequence – Random] X session [POST – PRE]). In PD patients, increase in VO_2max (indicating improved aerobic fitness as a result of training) correlated positively and significantly with increase activity in the hippocampus bilaterally (Table 2. Fig. 2) and the left dorsal striatum. This indicated that as the aerobic capacity improved in PD patients, the motor learning specific activation also increased in these brain regions. In contrast, a significant negative correlation was observed in bilateral cerebellum lobe 7, 8 and 9 (Table 2. Fig. 2).

3.2.2. Functional brain changes related to motor learning capacity following AET in HC

The main learning effect [Sequence – Random] by session [POST – PRE] assessed within the HC group revealed no significant change in activity between sessions. The regression analysis [Sequence – Random] X session [POST – PRE] also revealed no significant correlation between AET-related changes in aerobic capacity and brain changes related to motor learning capacity for HC group alone.

3.2.3. Between group differences in functional brain activity related to motor learning capacity following AET

When comparing the two groups (PD vs. HC) on the main learning effect [Sequence – Random] by session [POST – PRE], PD patients showed significantly higher levels of motor learning related activation than HC, post-AET as compared to pre-AET, in the left cerebellum

(lobules 8 and 9), right globus pallidus, and left ventral striatum (Table 3, Fig. 3). The left hippocampus was marginally significant (0.06) in this contrast. However, no significant differences were found in the opposite direction (i.e., HC greater than PD) for the same contrast.

3.2.4. Functional brain changes following AET in PD and HC regressed against changes in aerobic fitness

Between-group differences in regression between VO2max changes and MSL-related brain activity changes were observed in the right hippocampus (Table 3, Fig. 4) and in left cerebellum lobules 8, 9 and 7 (negative correlation). These between-group effects were both driven by the findings in the PD group. Again, no significant differences were found in the opposite direction (i.e., HC greater than PD).

4. DISCUSSION

We recently reported that 12 weeks of progressive intense AET resulted in significant improvement in aerobic fitness as well as motor skill learning in both PD and HC groups (Duchesne et al., 2015). AET-related MSL improvements were global in HC individuals as they were observed in both conditions (sequence and random), but were specific to the sequence condition in PD patients. In addition, PD patients improved their sequence-specific motor learning capacity after aerobic training as indicated by the significant difference between sequence and random conditions after the training period only. Interestingly, in the present study, the neuroimaging results corroborate those behavioral findings and suggest that AET-related changes in motor sequence learning capacity (i.e., difference between sequence and random conditions) are mainly seen in PD individuals. Specifically, increases in MSL-specific

brain activity due to training were found in the temporal lobe, hippocampus, striatum and cerebellum in the PD group. Importantly, there was also a positive relation between the patients' change in aerobic fitness and MSL-related changes in the hippocampal and striatal activity, while we found a negative relation between the change in fitness level and activity in the cerebellum in PD patients. Most importantly, the effects at the cerebral level are larger in the PD than in the HC group

MSL exercise-dependent plasticity related to the striatum and hippocampus in PD individuals.

The current study is the first to examine the changes in neural substrate supporting MSL following aerobic exercise training in both healthy controls and PD patients. Our findings thus extend the neuroimaging literature on implicit MSL in PD individuals and HC participants (Gamble et al., 2014; Ruitenberg et al., 2015; Siegert et al., 2006), by specifically highlighting the positive effects of AET on the MSL-related activity in the striatum, cerebellum and hippocampus; all structures that are typically involved in motor learning (Albouy, King, Maquet et Doyon, 2013; Doyon et al., 2009; Doyon et al., 2011b). In fact, our hypothesis regarding changes in MSL specific to striatal changes following AET was confirmed in PD individuals. This finding is consistent with previous studies, which have revealed AET-dependent neuroplasticity in the central nervous system due to neurochemical changes in the striatum, the latter having been proposed as one possible mechanism of action to explain the gains in performance on motor tasks in PD (Petzinger et al., 2011; Petzinger et al., 2013b; Petzinger et al., 2015). Indeed, research in animal models of PD using dopaminergic neurotoxins has shown that behavioral motor ameliorations following physical exercise are associated with increased

efficiency in dopaminergic and glutamatergic neurotransmission (Fisher et al., 2013; Paillard et al., 2015; Petzinger et al., 2013b; Petzinger et al., 2010; Petzinger et al., 2015), which together are thought to reduce the cortically-driven hyper-excitability observed in PD patients. These authors have reported an increase in dopamine availability coupled with a greater expression of dopamine D2 receptors, hence producing a better dopaminergic signaling in the striatum overall. Furthermore, physical exercise has been found to diminish the amount of synaptic glutamate release, which is known to decrease the level of cortical excitability (Fisher et al., 2004). Although conjectural, it is thus probable that the AET-specific changes in striatal activity observed in the current study may reflect this type of neurochemical mechanism, which would in turn explain the improvement in motor learning.

Interestingly, our results revealed that AET-related and MSL-specific functional brain changes are not only observed in the striatum, but within the hippocampus and cerebellum as well. These findings could suggest that such brain structures are part of the functional network compensating for the typical dysfunction within the cortico-striatal circuits seen in PD. In fact, the reported positive relationship between changes in aerobic fitness and AET-related MSL brain changes in the hippocampus and the striatum is consistent with emerging data suggesting that links between the hippocampus and the dopaminergic systems in PD are important in memory and learning (Calabresi, Castrioto, Di Filippo et Picconi, 2013). In their review, Calabresi et al. (2013) suggested that, while dopamine-dependent impairment (involving a complex molecular dysfunction at glutamatergic synapses) of hippocampal long-term potentiation (LTP) might contribute to cognitive impairments in PD, such interactions could also be a potential source of symptoms reduction in PD patients. Clinical interventions

such as AET, for example, could potentially stimulate neurogenesis in the dysfunctional hippocampus of PD's individuals, as it been shown in rodent's studies (Pereira et al., 2007; Voss, Vivar, Kramer et van Praag, 2013). This type of interventions could also be responsible for the associated involvement of neurotrophic factors, as a greater expression in brain-derived neurotrophic factor (BDNF) and LTP mechanisms following exercise has also been proposed as a putative mechanism responsible for the neuroprotective effects and functional improvements in this clinical population (Audiffren et al., 2011; Dishman et al., 2006; Fabel et Kempermann, 2008; Gomez-Pinilla et al., 2011; Mustroph et al., 2012; Voss, Vivar, Kramer et van Praag). Based on evidence that exercise-dependent brain changes within the hippocampus have been associated with functional changes in memory (Erickson et al., 2011; Szabo et al., 2011), we can thus conjecture that the improvement observed during MSL in PD following AET could be explained by LTP-like processes, due to greater expression of BDNF in the hippocampus.

In light of these recent findings (Calabresi et al., 2013), it can be hypothesized that the beneficial effect that AET has on MSL-related activity in both of these regions, may be based on the interaction or functional connectivity between them. It is possible that plastic AET- and MSL-related changes may first occur within the hippocampus, and then propagate in basal ganglia via interactions between the MTL and dopaminergic system. This assumption is based on the fact that while MSL-related changes were observed in both hippocampus and striatum in PD individuals, only the hippocampal changes remained positively correlated with improvements in aerobic fitness when PD and HC participants were compared. Yet further

functional connectivity investigations are still necessary to elucidate such AET-related brain reorganisation.

MSL exercise-dependent plasticity related to the cerebellum in PD individuals

In the current study, we found that AET-related and MSL specific changes in the cerebellum correlated negatively with changes in aerobic capacity. Although apparently contradictory, this result can be interpreted in light of several lines of evidence from previous studies: First, changes in the cerebellum have been interpreted as a compensatory functional system in animal models of PD model following exercise (Holschneider, Yang, Guo et Maarek, 2007; Wang, Guo, Myers, Heintz et Holschneider, 2015b; Wang, Guo, Myers, Heintz, Peng, et al., 2015), and a similar assumption has been proposed following striatal dysfunction in PD (Doyon, 2008). Second, human studies have indicated that both the cortico-striatal (CS) and cortico-cerebellar (CC) systems play distinctive roles in MSL (Doyon, 2008; Doyon et Benali, 2005a; Doyon et al., 2003; Leggio et Molinari, 2015), despite the fact that cerebellum and basal ganglia are known to be interconnected (Bostan et Strick, 2010b; Hoshi, Tremblay, Feger, Carras et Strick, 2005). Given the interaction between the CC and CS systems during MSL (Doyon, 2008; Doyon et al., 2009; Doyon et Benali, 2005a) and the fact that previous functional imaging data revealed that cerebellar hemispheres are hyperactivated, while the striatum is hypoactivated in PD patients as compared to healthy controls (Yu, Sternad, Corcos et Vaillancourt, 2007), it is thus possible that the cerebellum is capable of compensating for the deficient basal ganglia activity observed in PD. Hence, in the current study, the PD participants who did not improve their aerobic capacity used predominantly the cerebellum during MSL,

whereas those who showed significant changes in aerobic fitness used the hippocampus and striatum, indicating a 'restoration' of functionality in the network typically seen in MSL.

According to the motor sequence learning literature, both the cerebellum and striatum are known to be involved in the early MSL phase, while only the striatum has been shown to maintain its activity in later learning stages when the memory trace has been consolidated (Doyon et al., 2009; Doyon et al., 2011a; Doyon et al., 2002). Therefore, while modest improvements in aerobic capacity linked with increases in cerebellar activity may reflect learning in the early stage tested here, the fact that large improvements in aerobic fitness were associated with an enhanced hippocampal and striatal functioning may reflect a transition towards a more durable stage of MSL. These MSL findings are thus in line with previous structural and physiological investigations, which parallel the functional changes that aerobic exercise can exert in general (e.g.,(Hillman, Erickson et Kramer, 2008) for a review), and in PD, in particular (Ahlskog, 2011; Alberts, Linder, Penko, Lowe et Phillips, 2011; Goodwin et al., 2008; Hirsch et Farley, 2009b; Speelman et al.) for reviews).

MSL and exercise in HC individuals

Compared to PD individuals, AET did not have a statistically significant effect on changes in the neural correlates of MSL in the HC group. Such divergence between the HC and PD groups could be explained by a potential ceiling effect observed at baseline for the HC group in regards to their MSL capacity at both the behavioural and cerebral level. Given that HC individuals already showed a good MSL capacity prior to AET, they obviously had less room for sequence-specific behavioural improvement compared to PD patients. This is supported by the fact that analysis of the behavioral results revealed that, while HC individuals improved their

motor performance in both random and sequence condition after AET, they also maintained a similar magnitude in RT difference between these two conditions (Duchesne et al., 2015). This pattern of results can be interpreted as HC individuals having a more efficient medial temporal lobe, CS, CC functioning networks prior to AET, as compared to PD patients, which leaves also less room for improvements to be seen in functional activity in these brain areas

5. LIMITATIONS AND CONCLUSIONS

One of the limitations in our study was the heterogeneity of the patient population. Similar to many other studies with PD patients, disease characteristics were diverse (e.g., motor, cognitive, neuropsychiatric, etc.). In fact, it was often a challenge to control for all symptoms and obtain a homogeneous sample. However, we used several strategies to address this limitation. First, we matched the PD group with the HC group with respect to sex distribution, age, years of education, cognitive and fitness level. In addition, given that the two groups differed in their depression and anxiety symptoms, we accounted for these variables in our statistical analyses by considering them as covariates in the analyses of the behavioural data. Another limitation of our study was the lack of a PD control group for the type of exercise. Despite this constraint, however, the fact that we conducted a regression analysis highlighting functional brain changes in relation with aerobic fitness level of improvement allowed us to ensure that the brain changes were specific to the AET program.

To conclude, this study is the first to assess the neural correlates of MSL following AET in PD. Functional reorganisation of brain activity in early PD following aerobic training was observed within the hippocampus, the striatum and the cerebellum, resulting in improvement

of their learning capacity. Most importantly, MSL specific brain plasticity correlated with changes in aerobic fitness, showing a positive relationship with the hippocampus and the striatum and a negative relationship with the cerebellum. Altogether our study makes two important contributions to the field. First, we show that a 12-week progressive aerobic training regimen has beneficial effects on motor skill learning in sedentary PD and healthy individuals. Second, we highlight the neurophysiological changes underlying exercise-dependent plasticity in PD, with particular emphasis on the neuronal substrate of MSL. Our results thus pave the way for other studies to further explore the structural and functional organization within brain regions and how exercise-dependent plasticity manifests itself within the medial temporal lobe, CS and CC systems following chronic or acute bouts of aerobic activities in PD. As a result, these findings have important clinical implications for the rehabilitation of PD individuals, as the design and the use of non-pharmacological interventions based on physical exercise can be implemented to improve motor learning capacity and restore motor functions in patients afflicted with this debilitating disease.

ACKNOWLEDGMENTS

1. This work was supported by the Fonds de Recherche Santé Québec under Grant 26409.

2. The authors wish to thank Dr. Juan Manuel Villalpando and Dr. Thien Tuong Minh Vu who kindly accepted to supervise physical assessment during testing.

REFERENCES:

Ahlskog, J. E. (2011). Does vigorous exercise have a neuroprotective effect in Parkinson disease? *Neurology, 77*(3), 288-294.

Alberts, J. L., Linder, S. M., Penko, A. L., Lowe, M. J. et Phillips, M. (2011). It is not about the bike, it is about the pedaling: forced exercise and Parkinson's disease. *Exerc Sport Sci Rev, 39*(4), 177-186. doi: 10.1097/JES.0b013e31822cc71a

Albouy, G., Fogel, S., King, B. R., Laventure, S., Benali, H., Karni, A., . . . Doyon, J. (2015). Maintaining vs. enhancing motor sequence memories: respective roles of striatal and hippocampal systems. *Neuroimage, 108*, 423-434. doi: 10.1016/j.neuroimage.2014.12.049

Albouy, G., King, B. R., Maquet, P. et Doyon, J. (2013). Hippocampus and striatum: dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation. *Hippocampus, 23*(11), 985-1004. doi: 10.1002/hipo.22183

Amano, S., Roemmich, R. T., Skinner, J. W. et Hass, C. J. (2013). Ambulation and Parkinson disease. *Phys Med Rehabil Clin N Am, 24*(2), 371-392. doi: 10.1016/j.pmr.2012.11.003

American College of Sport Medicine (2006). *ACSM's Guidelines for exercise testing and prescription sixth edition*. USA, Philadelphia: Lippincott Williams & Wilkins, Lea & Febiger.

Audiffren, M., André, N. et Albinet, C. (2011). Effets positifs de l'exercice physique chronique sur les fonctions cognitives des seniors: bilan et perspectives. *Revue de neuropsychologie neurosciences cognitives et cliniques, 3*(4), 207-225.

Beall, E. B., Lowe, M. J., Alberts, J. L., Frankemolle, A. M. M., Thota, A. K., Shah, C. et Phillips, M. D. (2013). The Effect of Forced-Exercise Therapy for Parkinson's Disease on Motor Cortex Functional Connectivity. *Brain Connectivity, 3*(2), 190-198. doi: 10.1089/brain.2012.0104

Beck, A. T. et Beamesderfer, A. (1974). Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry, 7*(0), 151-169.

Bostan, A. C. et Strick, P. L. (2010). The cerebellum and basal ganglia are interconnected. *Neuropsychol Rev, 20*(3), 261-270.

Calabresi, P., Castrioto, A., Di Filippo, M. et Picconi, B. (2013). New experimental and clinical links between the hippocampus and the dopaminergic system in Parkinson's disease. *Lancet Neurol, 12*(8), 811-821. doi: 10.1016/S1474-4422(13)70118-2

Carbon, M., Reetz, K., Ghilardi, M. F., Dhawan, V. et Eidelberg, D. (2010). Early Parkinson's disease: longitudinal changes in brain activity during sequence learning. *Neurobiol Dis, 37*(2), 455-460.

Clark, G. M., Lum, J. A. G. , and Ullman, M. T. . (2014). A meta-analysis and meta-regression of serial reaction time tast performance in Parkinson's disease. *Neuropsychology*.

Dishman, R. K., Berthoud, H. R., Booth, F. W., Cotman, C. W., Edgerton, V. R., Fleshner, M. R., . . . Zigmond, M. J. (2006). Neurobiology of exercise. *Obesity (Silver Spring), 14*(3), 345-356.

Doyon, J. (2008). Motor sequence learning and movement disorders. *Curr Opin Neurol, 21*(4), 478-483.

Doyon, J., Bellec, P., Amsel, R., Penhune, V., Monchi, O., Carrier, J., . . . Benali, H. (2009). Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav Brain Res, 199*(1), 61-75. doi: 10.1016/j.bbr.2008.11.012

Doyon, J. et Benali, H. (2005). Reorganization and plasticity in the adult brain during learning of motor skills. *Curr Opin Neurobiol, 15*(2), 161-167. doi: 10.1016/j.conb.2005.03.004

Doyon, J., Orban, P., Barakat, M., Debas, K., Lungu, O., Albouy, G., . . . Benali, H. (2011a). [Functional brain plasticity associated with motor learning.]. *Med Sci (Paris), 27*(4), 413-420.

Doyon, J., Orban, P., Barakat, M., Debas, K., Lungu, O., Albouy, G., . . . Benali, H. (2011b). [Functional brain plasticity associated with motor learning]. *Med Sci (Paris), 27*(4), 413-420. doi: 10.1051/medsci/2011274018

Doyon, J., Penhune, V. et Ungerleider, L. G. (2003). Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia, 41*(3), 252-262.

Doyon, J., Song, A. W., Karni, A., Lalonde, F., Adams, M. M. et Ungerleider, L. G. (2002). Experience-dependent changes in cerebellar contributions to motor sequence learning. *Proc Natl Acad Sci U S A, 99*(2), 1017-1022. doi: 10.1073/pnas.022615199

Duchesne, C., Lungu, O., Nadeau, A., Robillard, M. E., Bore, A., Bobeuf, F., . . . Doyon, J. (2015). Enhancing both motor and cognitive functioning in Parkinson's disease: Aerobic exercise as a rehabilitative intervention. *Brain Cogn, 99*, 68-77. doi: 10.1016/j.bandc.2015.07.005

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A, 108*(7), 3017-3022. doi: 10.1073/pnas.1015950108

Fabel, K. et Kempermann, G. (2008). Physical Activity and the Regulation of Neurogenesis in the Adult and Aging Brain. *NeuroMolecular Medicine, 10*(2), 59-66.

Fisher, B. E., Li, Q., Nacca, A., Salem, G. J., Song, J., Yip, J., . . . Petzinger, G. M. (2013). Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. *NeuroReport, 24*(10), 509-514. doi: 10.1097/WNR.0b013e328361dc13

Fisher, B. E., Petzinger, G. M., Nixon, K., Hogg, E., Bremmer, S., Meshul, C. K. et Jakowec, M. W. (2004). Exercise-induced behavioral recovery and neuroplasticity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse basal ganglia. *J Neurosci Res, 77*(3), 378-390.

Gamble, K. R., Cummings, T. J., Jr., Lo, S. E., Ghosh, P. T., Howard, J. H., Jr. et Howard, D. V. (2014). Implicit sequence learning in people with Parkinson's disease. *Front Hum Neurosci, 8*, 563. doi: 10.3389/fnhum.2014.00563

Gillian M. Clark, J. A. G. L., and Michael T. Ullman. (2014). A meta-analysis and meta-regression of serial reaction time tast performance in Parkinson's disease. *Neuropsychology*.

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., . . . LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders, 23*(15), 2129-2170. doi: 10.1002/mds.22340

Gomez-Pinilla, F., Zhuang, Y., Feng, J., Ying, Z. et Fan, G. (2011). Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *European Journal of Neuroscience, 33*(3), 383-390.

Goodwin, V. A., Richards, S. H., Taylor, R. S., Taylor, A. H. et Campbell, J. L. (2008). The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov Disord, 23*(5), 631-640.

Herman, T., Giladi, N., Gruendlinger, L. et Hausdorff, J. M. (2007). Six weeks of intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil, 88*(9), 1154-1158.

Hillman, C. H., Erickson, K. I. et Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci, 9*(1), 58-65.

Hirsch, M. A. et Farley, B. G. (2009). Exercise and neuroplasticity in persons living with Parkinson's disease. *Eur J Phys Rehabil Med, 45*(2), 215-229.

Holschneider, D. P., Yang, J., Guo, Y. et Maarek, J. M. (2007). Reorganization of functional brain maps after exercise training: Importance of cerebellar-thalamic-cortical pathway. *Brain Res, 1184*, 96-107. doi: 10.1016/j.brainres.2007.09.081

Hoshi, E., Tremblay, L., Feger, J., Carras, P. L. et Strick, P. L. (2005). The cerebellum communicates with the basal ganglia. *Nat Neurosci, 8*(11), 1491-1493. doi: http://www.nature.com/neuro/journal/v8/n11/suppinfo/nn1544_S1.html

Jackson, A. S., Blair, S. N., Mahar, M. T., L.T., W., Ross, R. M. et Stuteville, J. E. (1990). Prediction of functional aerobic capacity without exercise testing. *Medicine & Science in Sports & Exercise, 22*(6), 863-870.

Leggio, M. et Molinari, M. (2015). Cerebellar Sequencing: a Trick for Predicting the Future. *The Cerebellum, 14*(1), 35-38. doi: 10.1007/s12311-014-0616-x

Mang, C. S., Snow, N. J., Campbell, K. L., Ross, C. J. et Boyd, L. A. (2014). A single bout of high-intensity aerobic exercise facilitates response to paired associative stimulation and promotes sequence-specific implicit motor learning. *J Appl Physiol (1985), 117*(11), 1325-1336. doi: 10.1152/japplphysiol.00498.2014

Mustroph, M. L., Chen, S., Desai, S. C., Cay, E. B., DeYoung, E. K. et Rhodes, J. S. (2012). Aerobic exercise is the critical variable in an enriched environment that increases hippocampal neurogenesis and water maze learning in male C57BL/6J mice. *Neuroscience, 219*, 62-71. doi: 10.1016/j.neuroscience.2012.06.007

Nadeau, A., Pourcher, E. et Corbeil, P. (2014). Effects of 24 wk of Treadmill Training on Gait Performance in Parkinson's Disease. *Medicine & Science in Sports & Exercise, 46*(4), 645-655 610.1249/MSS.0000000000000144.

Nazem, S., Siderowf, A. D., Duda, J. E., Ten Have, T., Colcher, A., Horn, S. S., . . . Weintraub, D. (2009). Montreal Cognitive Assessment Performance in Patients with Parkinson's Disease with "Normal" Global Cognition According to Mini-Mental State Examination

Score. *Journal of the American Geriatrics Society, 57*(2), 304-308. doi: 10.1111/j.1532-5415.2008.02096.x

Nissen et Bullemer. (1987). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology 19*(1), 32.

Osman, A., Kopper, B. A., Barrios, F. X., Osman, J. R. et Wade, T. (1997). The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. *J Clin Psychol, 53*(1), 7-14.

Paillard, T., Rolland, Y. et de Souto Barreto, P. (2015). Protective Effects of Physical Exercise in Alzheimer's Disease and Parkinson's Disease: A Narrative Review. *J Clin Neurol, 11*(3), 212-219.

Petzinger, G. M., Fisher, B. E., Akopian, G., Holschneider, D. P., Wood, R., Walsh, J. P., . . . Jakowec, M. W. (2011). The role of exercise in facilitating basal ganglia function in Parkinson's disease. *Neurodegener Dis Manag, 1*(2), 157-170.

Petzinger, G. M., Fisher, B. E., McEwen, S., Beeler, J. A., Walsh, J. P. et Jakowec, M. W. (2013). Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol, 12*(7), 716-726. doi: 10.1016/S1474-4422(13)70123-6

Petzinger, G. M., Fisher, B. E., Van Leeuwen, J. E., Vukovic, M., Akopian, G., Meshul, C. K., . . . Jakowec, M. W. (2010). Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. *Mov Disord, 25 Suppl 1*, S141-145. doi: 10.1002/mds.22782

Petzinger, G. M., Holschneider, D. P., Fisher, B. E., McEwen, S., Kintz, N., Halliday, M., . . . Jakowec, M. W. (2015). The Effects of Exercise on Dopamine Neurotransmission in Parkinson's Disease: Targeting Neuroplasticity to Modulate Basal Ganglia Circuitry. *Brain Plast, 1*(1), 29-39.

Petzinger, G. M., Walsh, J. P., Akopian, G., Hogg, E., Abernathy, A., Arevalo, P., . . . Jakowec, M. W. (2007). Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. *J Neurosci, 27*(20), 5291-5300.

Physiology, C. S. f. E. (1996). *Professional Fitness Lifestyle Consultant 2*. Ottawa.

Pothakos, K., Kurz, M. J. et Lau, Y. S. (2009). Restorative effect of endurance exercise on behavioral deficits in the chronic mouse model of Parkinson's disease with severe neurodegeneration. *BMC Neurosci, 10*, 6.

Ridgel, A. L., Kim, C. H., Fickes, E. J., Muller, M. D. et Alberts, J. L. (2011). Changes in executive function after acute bouts of passive cycling in Parkinson's disease. *J Aging Phys Act, 19*(2), 87-98.

Ridgel, A. L., Vitek, J. L. et Alberts, J. L. (2009). Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil Neural Repair, 23*(6), 600-608.

Ruitenberg, M. F., Duthoo, W., Santens, P., Notebaert, W. et Abrahamse, E. L. (2015). Sequential movement skill in Parkinson's disease: A state-of-the-art. *Cortex, 65*, 102-112. doi: 10.1016/j.cortex.2015.01.005

Schendan, H. E., Tinaz, S., Maher, S. M. et Stern, C. E. (2013). Frontostriatal and mediotemporal lobe contributions to implicit higher-order spatial sequence learning

declines in aging and Parkinson's disease. *Behavioral Neuroscience, 127*(2), 204-221. doi: 10.1037/a0032012

Siegert, R. J., Taylor, K. D., Weatherall, M. et Abernethy, D. A. (2006). Is implicit sequence learning impaired in Parkinson's disease? A meta-analysis. *Neuropsychology, 20*(4), 490-495.

Speelman, A. D., van de Warrenburg, B. P., van Nimwegen, M., Petzinger, G. M., Munneke, M. et Bloem, B. R. (2011). How might physical activity benefit patients with Parkinson disease? *Nat Rev Neurol, 7*(9), 528-534. doi: 10.1038/nrneurol.2011.107

Szabo, A. N., McAuley, E., Erickson, K. I., Voss, M., Prakash, R. S., Mailey, E. L., . . . Kramer, A. F. (2011). Cardiorespiratory fitness, hippocampal volume, and frequency of forgetting in older adults. *Neuropsychology, 25*(5), 545-553. doi: 10.1037/a0022733

van Eijkeren, F. J. M., Reijmers, R. S. J., Kleinveld, M. J., Minten, A., Bruggen, J. P. t. et Bloem, B. R. (2008). Nordic walking improves mobility in Parkinson's disease. *Movement Disorders, 23*(15), 2239-2243.

van Nimwegen, M., Speelman, A., Hofman-van Rossum, E., Overeem, S., Deeg, D., Borm, G., . . . Munneke, M. (2011). Physical inactivity in Parkinson's disease. *Journal of Neurology*, 1-8.

Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T. et Kramer, A. F. (2011). Exercise, brain, and cognition across the life span. *J Appl Physiol, 111*(5), 1505-1513.

Voss, M. W., Vivar, C., Kramer, A. F. et van Praag, H. Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences, 17*(10), 525-544. doi: 10.1016/j.tics.2013.08.001

Voss, M. W., Vivar, C., Kramer, A. F. et van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences, 17*(10), 525-544. doi: http://dx.doi.org/10.1016/j.tics.2013.08.001

Wang, Z., Guo, Y., Myers, K. G., Heintz, R. et Holschneider, D. P. (2015). Recruitment of the prefrontal cortex and cerebellum in Parkinsonian rats following skilled aerobic exercise. *Neurobiology of Disease, 77*(0), 71-87. doi: http://dx.doi.org/10.1016/j.nbd.2015.02.020

Wang, Z., Guo, Y., Myers, K. G., Heintz, R., Peng, Y.-H., Maarek, J.-M. I. et Holschneider, D. P. (2015). Exercise alters resting-state functional connectivity of motor circuits in parkinsonian rats. *Neurobiology of Aging, 36*(1), 536-544. doi: 10.1016/j.neurobiolaging.2014.08.016

Werheid, K., Zysset, S., Müller, A., Reuter, M. et von Cramon, D. Y. (2003). Rule learning in a serial reaction time task: An fMRI study on patients with early Parkinson's disease. *Cognitive Brain Research, 16*(2), 273-284. doi: 10.1016/s0926-6410(02)00283-5

Yoon, M. C., Shin, M. S., Kim, T. S., Kim, B. K., Ko, I. G., Sung, Y. H., . . . Kim, C. J. (2007). Treadmill exercise suppresses nigrostriatal dopaminergic neuronal loss in 6-hydroxydopamine-induced Parkinson's rats. *Neurosci Lett, 423*(1), 12-17.

Yu, H., Sternad, D., Corcos, D. M. et Vaillancourt, D. E. (2007). Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage, 35*(1), 222-233. doi: S1053-8119(06)01175-X [pii] 10.1016/j.neuroimage.2006.11.047

Table 3. Article 2: Demographics of the two groups of participants

Variables [a]	HC (n=20)	PD (n=19)	p-value
Sex (male\female)	8\12	13\6	0,07[b]
Age (years)	64 (8.19)	59 (7.11)	0.06[c]
Education (years)	15.7 (2.36)	15.05 (2.78)	0.43[c]
Fitness [d]	2.1 (1.17)	1.84 (1.26)	0.51[c]
Cognition (MMSE\MOCA) [e]	29.18\28.56 (1.25\1.51)	28.4\27.21 (1.34\1.85)	0.275\0.08[c]
Depression [f]	4.8 (4.5)	10.5 (8.3)	*0.01[c]
Anxiety [f]	2.1 (2.7)	8.6 (8.4)	*0.002[c]
Hoehn & Yahr score	N\A	2 (0)	N\A
UPDRS total score	N\A	21.84 (6.16)	N\A
Years diagnosed	N\A	8.1 (9.12)	N\A

[a] Values represent mean (standard deviation), except for 'Sex', where values represent counts.
[b] *p*-value from chi-square test
[c] *p*-value from ANOVA
[d] Jackson's questionnaire assessing activity level at baseline
[e] 5 PD and 11 HC were assessed with MMSE and 14 PD and 9 HC with MOCA
[f] Beck depression inventory and Beck anxiety were used

Table 4. Article 2: Functional imaging results of the changes in the main learning effect following aerobic exercise training in PD

Area	X mm	Y mm	Z mm	K	Z	p_{svc}
2.1. Main effect of session on sequence learning [POST – PRE] X [Sequence – Random]						
PD						
Right Temporal Lobe	30	12	-36	92	3,85	0,002
Left Temporal Lobe	-30	12	-38	36	3,45	0,008
Left Striatum Ventral	-18	6	-12	48	3,76	0,003
Left Hippocampus	-34	-16	-12	99	3,66	0,004
Right Cerebellum Lobules 8 and 9	16	-46	-54	38	3,1	0,022
Left Cerebellum Lobules 8 and 9	-20	-42	-52	38	3,14	0,02
Right Cerebelum Crus 1	28	-72	-38	51	3,1	0,022
2.2. Main effect of session on sequence learning [POST – PRE] X [Sequence – Random] regressed against changes in VO_2 max						
Positive						
Left Hippocampus	-18	-34	-2	182	3,19	0,017
Left Hippocampus	-18	-24	-10	23	3,12	0,021
Right Hippocampus	36	-32	-8	170	3,4	0,01
Left Putamen Dorsal	-28	0	18	45	3,04	0,025
Negative						
Cerebellum Lobule 7	-2	-76	-24	167	3,98	0,001
Left Cerebellum Lobules 8 and 9	-4	-62	-36	65	3,17	0,018
	-16	-60	-46	110	3,11	0,021
Right Cerebellum Lobules 8 and 9	26	-64	-46	58	3,23	0,015

Statistical inferences were performed at a threshold of $P < 0.05$ after correction for multiple comparisons over small spherical volumes (SVC). K represents the number of voxels in each cluster reported (determined at a threshold of $p = 0.005$).

Figure 4. Article 2: Motor sequence learning effect in PD patients before and after aerobic training

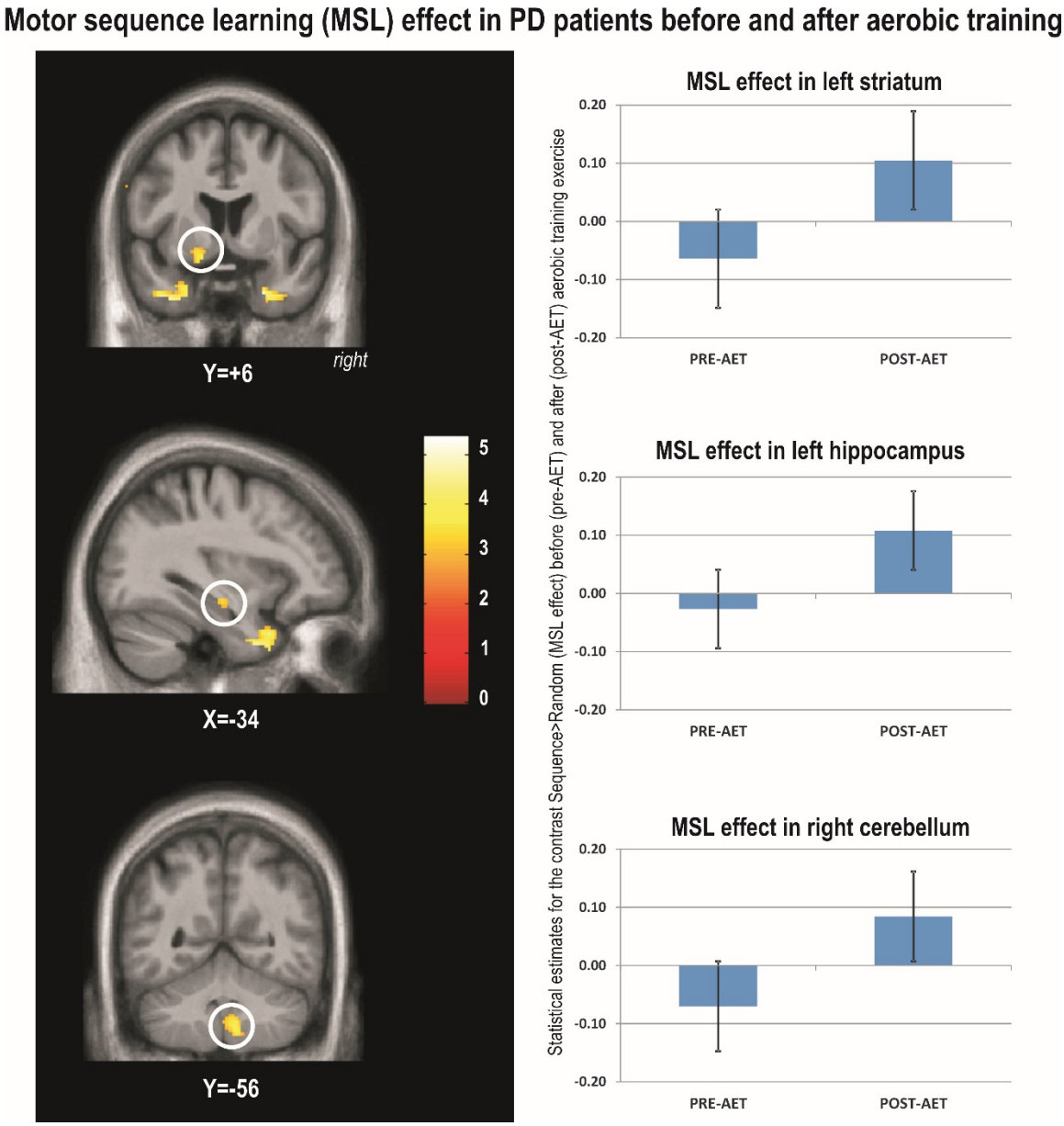


Figure 5. Article 2: Changes in aerobic fitness predict MSL-related changes in functional brain activity in PD patients

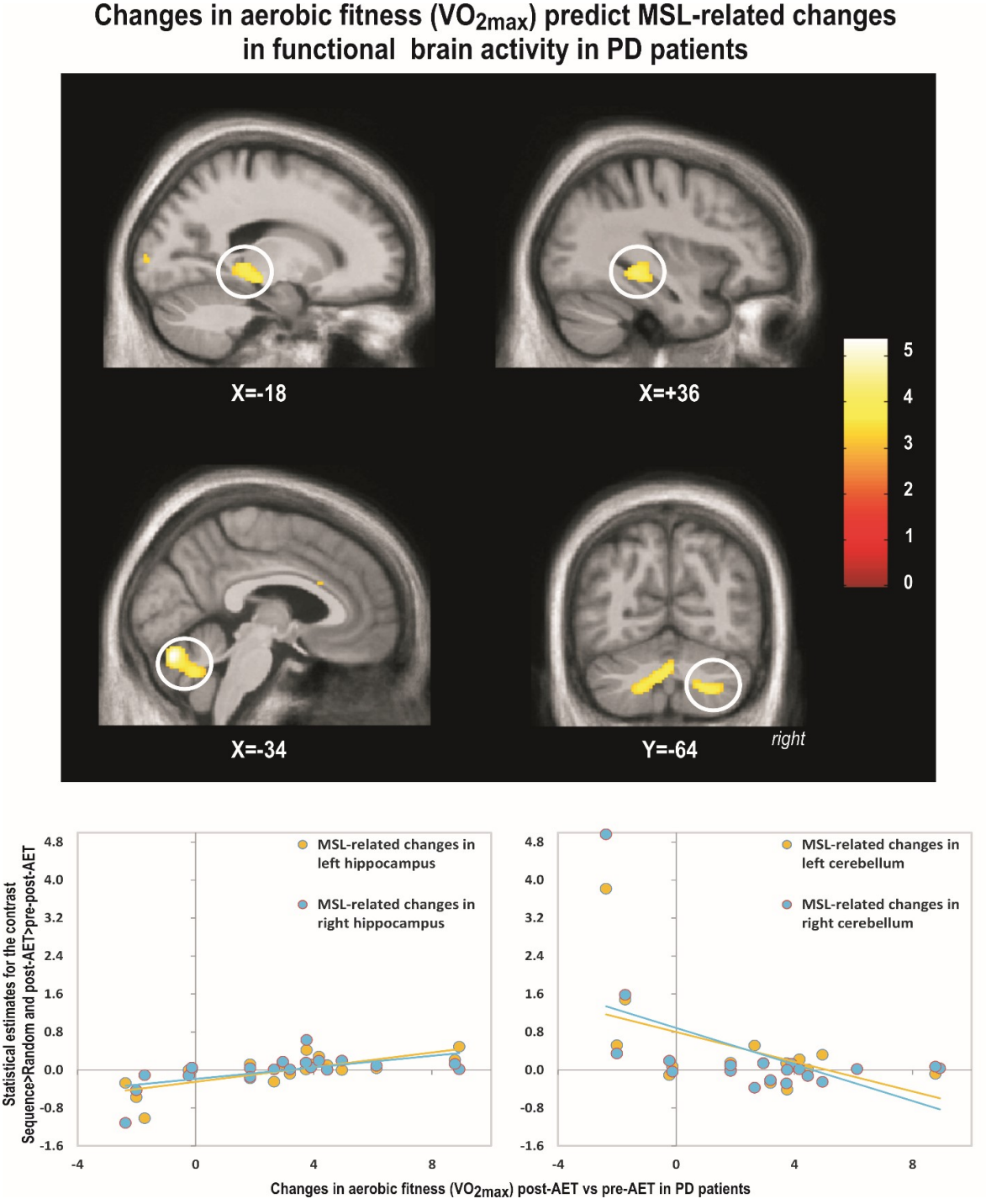


Table 3: Functional imaging results of the main sequence learning effect following aerobic exercise training between PD and HC.

Area	X mm	Y mm	Z mm	K	Z	p_{svc}
3.1. Main effect of session on sequence learning [POST – PRE] X [Sequence – Random]						
PD-HC						
Left Cerebellum Lobules 8 and 9	-2	-62	-40	95	3,5	0,007
	-20	-48	-54	181	3,41	0,009
	-24	-48	-44	169	3,3	0,013
Right Globus Pallidus	14	2	-10	11	3,15	0,019
Left Striatum Ventral	-18	6	-12	15	3,1	0,022
Left Hippocampus	-36	-16	-14	5	2,68	*0,06
HC-PD						
No significant responses						
3.2. Main effect of session on sequence learning [POST – PRE] X [Sequence – Random] regressed against changes in VO_2 max						
PD-HC						
Positive						
Right Hippocampus	20	-28	-6	38	3,15	0,019
Negative						
Cerebellum Lobule 7	-2	-76	-24	95	3,48	0,007
Left Cerebellum Lobules 8 and 9	0	-64	-32		2,85	0,041
HC-PD						
Positive						
No significant responses						
Negative						
No significant responses						

Statistical inferences were performed at a threshold of $P < 0.05$ after correction for multiple comparisons over small spherical volumes (SVC). K represents the number of voxels in each cluster reported (determined at a threshold of p = 0.005).

*Marginally significant

Figure 6. Article 2: Greater MSL-related functional brain changes in PD patients than in healthy controls after AET

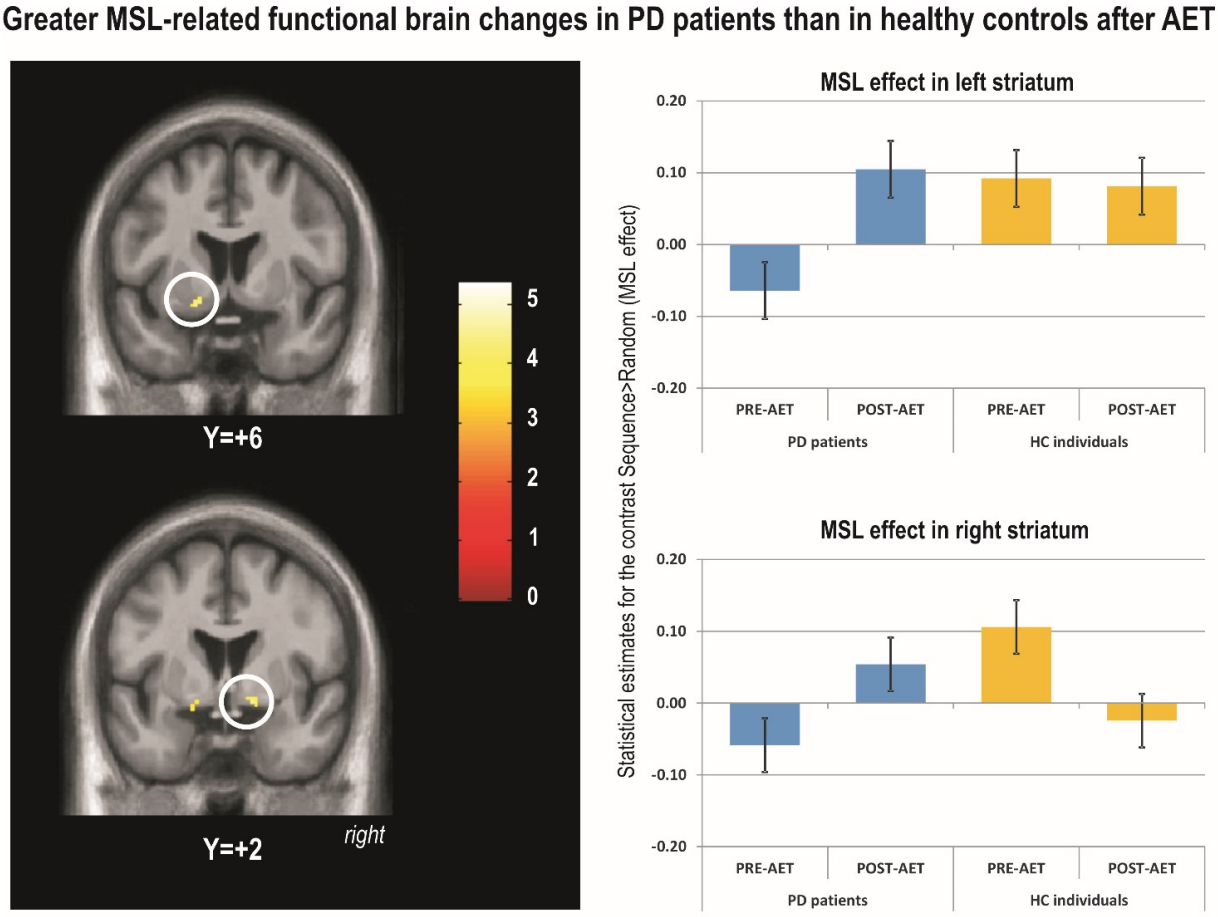
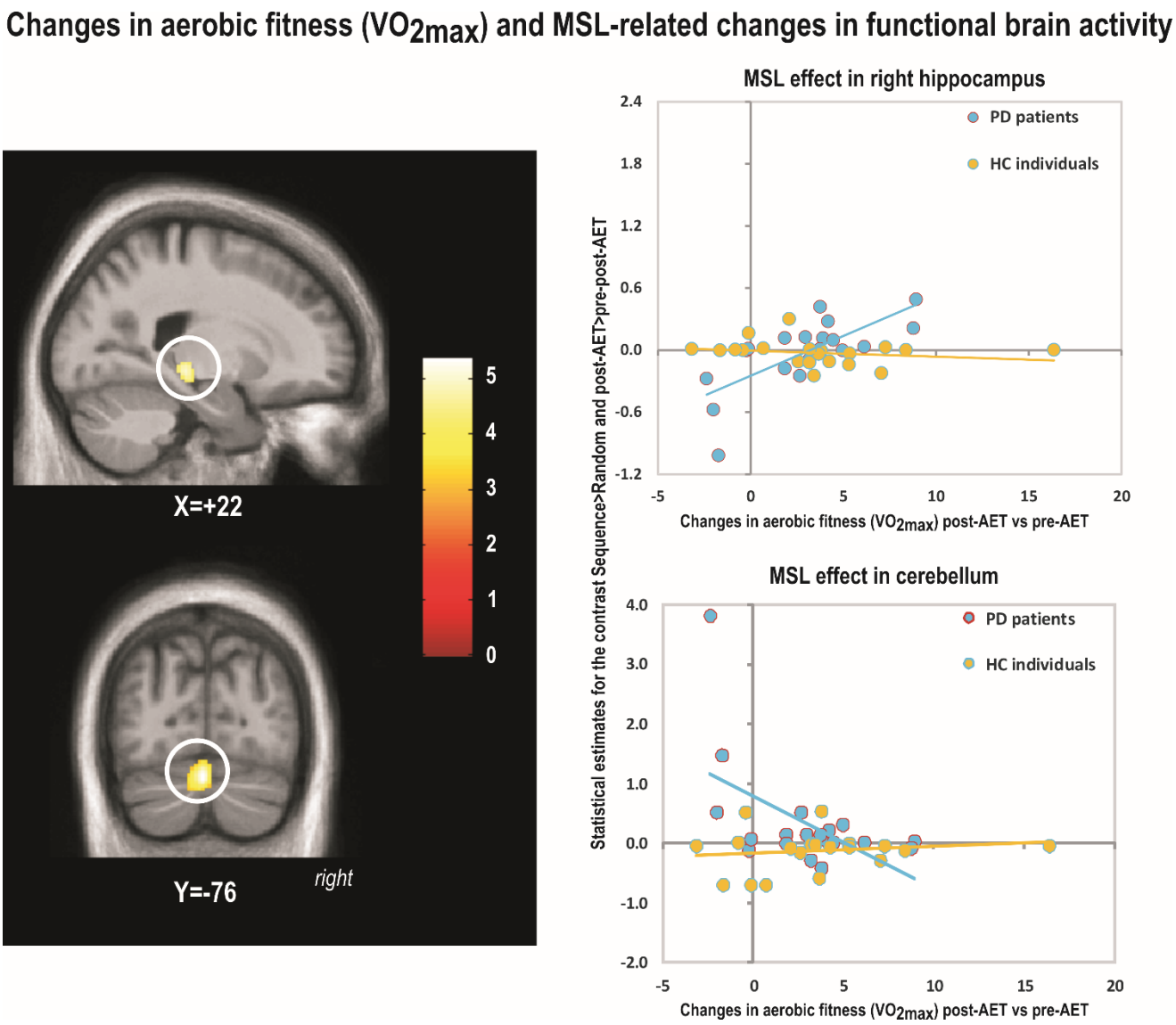


Figure 7. Article 2: Changes in aerobic fitness and MSL-related changes in functional brain activity



Chapter III: General Discussion

1. Introduction

Over the last two decades, PD's has been studied as a multi-system neurodegenerative disorder (Braak, Rub et Braak, 2000; Del Tredici et Braak, 2016). Accordingly, a significant number of studies in various domains (e.g., neuroimaging, kinesiology, psychology, etc.) have been conducted to expand our understanding of the disease, but also to advance efficiency of clinical treatment besides medication (e.g., L-Dopa) and surgical intervention (e.g. Deep Brain Stimulation). The present thesis aimed to advance knowledge on PD's by studying the effects of physical exercise as an adjunct treatment on a variety of cognitive and motor functions. More specifically, the study design was developed to investigate the impact of AET on cognitive functions (executive functions) as well as motor skill learning and its neural correlates in PD. The first article presents the effect of AET on MSL and cognition at the behavioural level. The second article emphasizes the effect of AET on MSL and its neurofunctional mechanisms. Finally, chapter III is organized to provide a broader reflection on the results reported in these two articles as well as to put forward ideas originating from the clinical experience acquired during the implementation of the current study. For instance, over the course of the recruitment process, the heterogeneity of PD's individuals was certainly evident in terms of the age onset (participants' age ranging from the thirties to over eighties), the presence of neuropsychiatric symptoms (anxiety and depression) and other physical manifestation of PD (tremor vs akinetic-rigidity). While this neurodegenerative disease is heterogeneous and complex in nature, physical exercise *per se* can also vary in

many different ways (e.g. type, dose, intensity). As such, the discussion first gives a summary of the results, then presents in two different sections the study's contributions and future avenues. Finally, as a mean to deepen reflections on studies' results, I then discuss the impact of PD symptom's heterogeneity and exercise variety on the perspective of prescribing exercise as a personalized form of treatment.

2. Summary of Results

AET has been shown to provide health benefits in individuals with PD. Yet, it was unknown to what extent AET can improve cognitive and motor skill learning to ensure an optimal daily functioning. In the first published article (Duchesne et al., 2015), I assessed the effects of a 3-month AET regimen on executive functions, procedural learning as well as on different health-related outcome measures. Twenty HC and 19 early PD individuals participated in a supervised, high intensity stationary recumbent bike training program (3 times/week; 12 weeks). Exercise prescription started at 20 minutes (+5 minutes/week up to 40 minutes) based on participant's maximal volume of oxygen uptake. Stroop and Trail making tests assessed the participants' inhibition and flexibility capacity, whereas participants' MSL was evaluated using an implicit version of the Serial Reaction Time Task. Results showed that the AET program was effective, as indicated by a significant improvement in aerobic capacity in all participants. Most importantly, AET improved inhibition and MSL significantly, but not flexibility.

In the second article, the focus was on the effect of AET on MSL and its neural correlates. Accordingly, MSL behavioural data and statistical analysis were the same as for the first paper; yet, the emphasis was on fMRI analysis performed before and after AET while subjects carried

out the implicit MSL task. Brain images revealed functional changes during MSL in the hippocampus, striatum and cerebellum in the group of PD patients, that is in areas known to contribute to the acquisition of a new sequence of movements. Importantly, the functional brain changes in PD individuals correlated also with changes in aerobic fitness; a positive relationship was found with increased activity in the hippocampus and striatum, while a negative relationship was observed with the cerebellar activity.

Results from both studies thus suggest that AET can be a valuable non-pharmacological intervention to promote, not only physical fitness in early PD, but also better cognitive functioning and MSL capacity.

3. Main scientific contributions

Certainly, results of this thesis make several important contributions to the field of neuropsychology/neuroscience. Notably, I believe that the interdisciplinary nature of the project was a very important strength. It not only allowed us to be innovative in the field, but to propose a solid experimental design. For instance, working with experts in the field of exercise (e.g. kinesiologist, physiologist) allowed us to implement a strong AET program with adequate supervision to respond to our clinical population's needs. Each collaborator nourished the foundation of knowledge in my thesis, and thus, this is why I think that the contributions presented in the next paragraphs are particularly meaningful for the field. The contributions presented in the next paragraphs have been organized in subsections: 1) Parkinson's disease cardiovascular health in comparison to healthy aging, 2) Parkinson's disease multidimensional nature (preservation of cognitive function and restoration of motor

function). As such, the next part will develop on the significance of each contribution to the field of neuropsychology/neuroscience.

3.1. Parkinson's Disease Cardiovascular Health in Comparison to Healthy Aging

A plethora of studies has demonstrated the benefits of AET on participants' aerobic capacity in healthy older subjects (Bherer et al., 2013b; Erickson et al., 2014; Gregory et al., 2013)for reviews). In recent years, there has also been a growing interest in studying AET in PD patients (Fisher et al., 2008; Herman et al., 2009; Hirsch et al., 2016; Monteiro et al., 2016). However, very few studies have investigated the effect of AET in PD in comparison to a healthy aging population, and thus this thesis contributes in filling such a gap in the literature. For instance, results reveal that PD's and HC's improved their aerobic capacity in a similar fashion following the 12-week (progressively intense) aerobic training regimen (see page 62, Figure 2.A.). Interestingly, the post VO_2max mean average for PD (27.7) is comparable to the pre VO_2max mean average for HC (28.1). These results suggest that cardiorespiratory health can be improved in PD individuals just as well as in HC. In addition, PD's aerobic capacity seems to normalize, or to be as close as expected from the normal (sedentary) aging group, as its gain is comparable to the initial HC's aerobic capacity following the AET program.

Altogether, our findings suggest that, although exercise for PD's patients can be physically, cognitively and affectively more demanding (because of the nature of the disease) than for HC's, the same pattern of results can be expected for both populations in terms of cardiovascular gains. In other words, it is possible to be healthy at the cardiorespiratory level despite suffering from PD. Such a statement is very meaningful for PD patients as this means

that we can expect that physical health will impact their psychological and social wellbeing (Eime, Young, Harvey, Charity et Payne, 2013). For instance, better cardiovascular health means that they will be having more energy (endurance) on a daily basis to fully engage in activities, nourishing a sense of self-efficacy and feeling of empowerment. In addition, for PD patients to be cardio-fit, this can possibly mean having all the benefit that's come along the ways, as observed in the normal aging population, such as a reduced cardio-metabolic risk, reduced risks of falls, improved cognitive functioning and functional capacity as well as a reduced risk of depression, anxiety, and dementia (Bauman et al., 2016).

Importantly, is the fact that exercise-dependent brain plasticity has been observed following AET in aging (Bherer, 2015), hence supporting the idea that PD can benefit, just as well as healthy older subjects, from AET at the brain level. In fact, the second article allows to characterize such plasticity following AET in PD, by comparing it to the neural changes observed in the normal aging group. As such, this between-group design allowed us to identify brain mechanisms that seem to be specific to exercise dependent plasticity in PD.

In sum, although more studies are required to specify in more details the benefits of cardiovascular health in PD's patients, the work reported in this thesis is one the first to demonstrate that, it is feasible to improve aerobic capacity of PD patients at the behavioural level in a fashion similar to the one observed within healthy aging individuals. Additionally, exercise dependent plasticity seems to involve different brain changes, or at least PD's specific brain changes in MSL function when compare to an HC group.

Besides studying the effect of AET in PD's compared to a HC's population, this thesis is also one of the first to report results demonstrating a relationship between the effects of exercise and changes in brain plasticity in a PD human study model. Interestingly, the PD's neural plasticity was related to the amount of cardiovascular improvement, and thus this finding supports the notion of exercise-dependent plasticity. From a scientific perspective, such contributions are very important to the field, as these results corroborate those of PD's animal studies supporting possible cerebral plastic changes underlying aerobic exercise in PD (Hirsch et Farley, 2009a; Hirsch et al., 2016). From a clinical perspective, it also implies that AET can influence the course of cardiovascular health in PD, and most probably the course of the disease within other functions (cognitive, motor), as describes in the next paragraphs.

3.2. Parkinson's Disease Multidimensional Nature

Many studies have been conducted in PD where they have investigated the effects of various treatment approaches (e.g. deep brain stimulation) on either motor (Rizek, Kumar et Jog, 2016) or non-motor symptoms (Cronin-Golomb, 2013; Goldman et Postuma, 2014; Reynolds et al., 2016). Out of these studies, a growing amount of research has been done on exercise and PD ((Petzinger et al., 2015; Shu et al., 2014; Uhrbrand et al., 2015) for review). However, none of them have studied the effect of AET on both the motor (MSL) and non-motor symptoms (cognition) of the disease, although, most activities of daily living involved the coordination of cognitive and motor functions. As such, it appears very important to study both functions together. This thesis contributed to disentangle such relationship. Accordingly, the work presented in this thesis brings an important contribution to the field as the parallel

assessment of these functions reflects the multidimensional nature of PD, hence representing an ecological point of view of the disease.

3.2.1. Preservation of Cognitive Functions

At the cognitive level, it is known that cognitive dysfunctions vary significantly in early PD (Monchi et al., 2016). In fact, our findings suggest that early PD and healthy aged individuals appear to function in a similar fashion (e.g., at the cognitive level) at first. However, as opposed to normal aging, the degenerative nature of PD leads undeniably to a cognitive deterioration, hence evolving into MCI (Yarnall, Rochester et Burn, 2013) and dementia conditions eventually (Xu, Yang et Shang, 2016). In that regard, even no cognitive change at all following a treatment can clinically be perceived as a positive outcome and as a cognitive preservation phenomenon. As such, results presented in this thesis are very encouraging for PD, as it is now conceivable that a non-pharmacological intervention, such as aerobic exercise, may improve cognitive functions, especially a significant capacity increase of inhibition in PD. Comparable to cardiovascular health, preserved executive functioning will contribute to sustain a better quality of life as well as a sense of self-efficacy and empowerment throughout the disease on a daily basis (van Uem et al., 2016). For instance, an improved inhibition capacity means that during daily activities (e.g., walking), PD's individuals can resist better to distraction (e.g., background sounds) than before AET. Consequently, an improved inhibition will reduce risk of falling, which is a common and devastating consequence of PD (Amboni, Barone et Hausdorff, 2013). Such finding also highlights the importance of good cognitive function (e.g. executive functions) on motor capacity (procedural learning). Although, distinct brain mechanisms

underlie both functions, they are quite interrelated as they both define the performance of an undertaken action.

Accordingly, the multidimensional representation of PD (motor and cognitive capacities) in this thesis is an important contribution to the field. First, results allow to identify that, for PD only, the effect of AET is somehow dependent of their initial motor and cognitive functioning. More specifically, individuals with poorer initial performance in both motor and cognitive domains will improve more in the motor, but less in the cognitive domain, whereas those with better initial performance will improve more on cognitive and less on motor area. These findings highlight the importance of using a personalised approach for treatment. In this instance, personalise prescription of exercise treatment according to symptomology will increase treatment efficiency. Furthermore, as results demonstrated, cognitive and motor functions are even more intertwined in PD, which bring forward the idea of possible mediating effect of each functions. Although this thesis was not designed for such investigations, it emphasises the importance of considering the initial state (e.g., specific symptomology) to improve treatment efficiency.

3.2.2. Restoration of Motor Functions

A paucity of literature exists on the effect of exercise on motor learning in PD and aging. This thesis is one of the first to study such effect on MSL in both populations. Given the present results, it is conceivable that a non-pharmacological intervention, such as aerobic exercise, can restore motor functions in PD. As for aging, the effect of AET does not seem to be specific to MSL, but to motor learning in general (execution and learning). On a daily basis, this means that despite motor symptomology (e.g. tremor, rigidity) in PD, AET appears to be an efficient

treatment to facilitate MSL. For instance, for PD's individuals AET is beneficial on commonly used procedural tasks, such as typing. This means that AET allows to alleviate day-to-day actions of PD individuals and to undertake new activities (e.g. piano), which again contributes to sustain a better quality of life and sense of self-efficacy and empowerment throughout the disease.

This thesis is not only one of the first to study MSL for both populations, but to provide results at the behavioural and neurofunctional levels. Accordingly, it allowed us to identify distinct learning patterns in PD patients. For instance, at the neurofunctional level, involvement of the globus pallidus following AET may be Indicative of a reorganisation in striatal PD dysfunction. As the dopaminergic dysfunction in early PD is first observed in the dorsal basal ganglia (Obeso et al., 2008), exercise dependent plasticity may act within preserved ventral basal ganglia area (globus pallidum vs striatum), representing a form of plasticity or compensatory mechanism. Furthermore, these functional mechanisms resulting from AET can be explained by an increased activity in areas (e.g. cerebellum) known to contribute to the acquisition of a new sequence of movements. Thus overall, this thesis contributes to highlight possible restorative motor learning mechanisms that seem to be specific to the effect of AET in PD. From a scientific perspective, these contributions are very important to the field, as they are in line with PD's animal studies supporting possible cerebral plastic changes with aerobic exercise in PD (Hirsch et al., 2016; Petzinger et al., 2015). From a clinical perspective, as cardiovascular health improved in PD, the course of the disease within other functions (cognitive, motor) can be preserved and restored, which are positive outcomes that have no price for PD individuals.

4. Future Avenues

4.1. Parkinson's Disease Heterogeneity

As mentioned in the introduction of the present general discussion and as described in demographics (see below, Table 5) of PD participants, PD's characteristics were diverse. For instances, PD participants in this study were mainly males (13) instead of females (6). The latter ratio is coherent with the higher incidence of PD found among males in the literature (Wooten, Currie, Bovbjerg, Lee et Patrie, 2004), with relative risk being 1.5 times greater in men than women. In addition, years of onset of the disease varied largely within this clinical population, as represented within this group of PD participants (standard deviation = 9 for years diagnosed) in demographic.

Table 5. Demographics of PD group of participants.

Variables [a]	**PD (n=19)**
Sex (male\female)	13\6
Age (years)	59 (7.11)
Education	15.05 (2.78)
Fitness [d]	1.84 (1.26)
Cognition (MMSE\MOCA) [e]	28.4\27.21 (1.34\1.85)
Depression [f]	10.5 (8.3)
Anxiety [f]	8.6 (8.4)
Hoehn & Yahr score	2 (0)
UPDRS total score	21.84 (6.16)
Years diagnosed	8.1 (9.12)

[a] Values represent mean (standard deviation), except for 'Sex', where values represent counts.

[d] Jackson's questionnaire assessing activity level at baseline

[e] 5 PD and 11 HC were assessed with MMSE and 14 PD and 9 HC with MOCA

[f] Beck depression inventory and Beck anxiety were used

Besides demographics, other characteristics also differed in PD's participants in the motor, cognitive and neuropsychiatric domains. Indeed, some participants suffered more significantly from tremors rather than rigidity (while other showed the reverse pattern), hence resulting into different subset of the UPDRS scores, despite the fact that they were all at the early stage of the disease (Hoehn and Yahr's stage 1-2). At the cognitive level, some patients exhibited also more difficulties than others, although they were no statistically significant differences within group. Finally, as mentioned (and controlled for) in both articles, a significant difference was found for depression and anxiety levels. Overall, this sample of PD participants represents quite well the ecological heterogeneous nature found in early PD (Monchi et al., 2016; Vogt Weisenhorn, Giesert et Wurst, 2016). Most importantly, despite this heterogeneity, significant patterns of results were obtained both at the behavioural and neurofunctional levels, hence providing evidence that AET in early PD results in positive outcomes. Nevertheless, it would be interesting for future studies to isolate the effect of each PD characteristics as it would possibly allow to detect subtle changes that were not observed in the present thesis (e.g. cognitive flexibility) or in the mediating/moderating effect.

4.2. Control Group

Although the original study design proposed for this thesis involved a randomized control trial with three groups, which included a PD group performing flexibility exercise, the difficult reality of clinical research went beyond our will, as the recruitment of PD individuals was a

challenge. Nevertheless, the study's design with two groups allowed to preserve statistical power (PD and matched normal control groups). Yet, it would be interesting in future studies to investigate the effect of other types of exercise (e.g. resistance exercise), as recent studies reported benefits of other types of exercise, for instance resistant training in PD (Roeder, Costello, Smith, Stewart et Kerr, 2015) and in normal aging (Liu-Ambrose et Donaldson, 2009). Nevertheless, results in this thesis provide strong evidence that AET is beneficial for cardiovascular, cognitive and motor capacities. The effects of aerobic exercise are not only observed at the behavioural level, but changes manifest itself within the brain (MSL) suggesting a form of plasticity within PD individuals. Again, it would be interesting to study if other types of exercise may facilitate the same or other plastic brain changes. In the same line of thoughts, cognitive changes (inhibition) may as well correlate with brain substrate (e.g. hippocampus?) and it would be meaningful to investigate further this avenue in PD as finding would help to personalize and improve treatment efficiency.

As a future perspective, it would also be interesting to study the effects of exercise on MSL that are specific to normal aging, as different behavioural results were presented in the HC group. Specifically, results in this thesis reported that subjects in the HC group improved on both conditions (Sequence and Random) following AET, which reflect an improvement in motor execution and MSL, as opposed to sequence learning improvement only in the PD group. Moreover, a good motor learning capacity was already observed before AET, representing a potential ceiling effect at the baseline (for HC); hence allowing little room for possible behavioural improvement in this group compared to the PD patients. Most

importantly, such ceiling effect also limits results with respect to the changes in neural network involvement. Specifically, the effect of exercise in HC improved motor skill learning (Sequence + Random) generally, but when measuring the effects of MSL (Sequence - Random) functional brain networks may be cancelled out by an overall improvement in both sequence and random conditions. Nevertheless, results in this thesis allows to report that AET is beneficial for HC, however, the manifestation of improvement observed between the PD group is different at the behavioural and neuronal levels in regards to MSL. Further investigation on the effect of exercise on MSL in normal aging would be an interesting avenue as it could detect subtle changes specific to normal aging. As such, it could be interesting, for instance, to have a study design with two HC groups, (HC-AET and HC-no exercise) to identify changes specific to normal aging.

5. Further Reflections on Parkinson's Disease Heterogeneity and Exercise Variety

At this point, prior thesis's sections have highlighted the undeniable heterogeneity of PD. This reality was also present in this thesis, hence, representing an ecological nature of early multidimensional PD's symptomology. Then, I have presented the benefits of AET in PD with a current perspective of the exercise aging literature. Although this project's aim was to investigate the effect of AET in PD, I thought it would be interesting to present a broader perspective of PD heterogeneity (subtypes) and exercise (e.g., type, intensity). Accordingly, the next sections will discuss further ideas on PD and exercise, as it may be helpful to personalised such treatment in PD.

5.1. Perspective on Parkinson's Disease Subtypes

5.1.1. Motor Symptoms

Different subtypes of PD's have been studied based on variance in the severity of disease's symptomology, such as the early versus late onset of the disease, the rapid versus slow disease progression, or the akinetic-rigidity predominant (non-tremor) versus tremor predominance (Thenganatt et Jankovic, 2014; van Rooden et al., 2011). To date, the literature on PD motor subtypes has established strong evidence that brain organization within the CS and CC systems differs, especially in the sub-group of PD patients characterized by tremor versus akinetic/rigid predominance (Lewis et al., 2011; Rajput, Voll, Rajput, Robinson et Rajput, 2009; Schapira et Schrag, 2011; Thenganatt et Jankovic, 2014; Zhang, Liu, Chen et Liu, 2014; Zhang et al., 2015). For instance, Zhang et al. (2015) have demonstrated that neural activity patterns in these two types of PD subgroups are both altered in regions involved in the default-mode network and the striatum. Moreover, the results reveal that the akinetic-rigid patients exhibit central neural activity changes in the mesolimbic cortex (amygdala), while the tremor dominant patients' brain activity is greater in the cerebellar regions. While altered CS system observed in both subtypes is the hallmark of PD nigro-striatal dopaminergic loss, involvement of the cerebellar (tremor) and mesolimbic (akinetic-rigid) regions provide further support on distinct brain mechanisms based on PD subtypes. More specifically, while the default-mode network and CS pathway are both implicated in akinetic-rigid and tremor subgroups, the neural activity within the mesolimbic-striatal circuit (akinetic-rigid) and CC loop (tremor) contribute separately to PD's symptomology. Such results raise a question as to whether the CC system involvement is recruited in PD to compensate for the CS dysfunction, or whether

the observed changes in cerebellar activity arise from one large neuronal dysfunction. In both cases, the cerebellar regions are of major importance to refine our understanding of such complex disease, but mostly to prescribe treatment, such as exercise in accordance with individual's symptoms (e.g. tremors vs rigidity). For instance, in the present thesis, the effect of AET on MSL implicated neural activity within the cerebellum, the striatum and the hippocampus. Most importantly, a positive relationship with AET was found with increased activity in the hippocampus and striatum, while a negative relationship was observed with the cerebellar activity. These results may be explained partly by the heterogeneity of motor symptoms (tremor, rigidity) in the population studied (higher representation of akinetic-rigid vs tremor), as it is possible that the impact of exercise within the brain act according to symptomology. Alternatively, the negative correlation could be due to the fact that subjects are learning and we know that activity within the cerebellum goes down with learning. As such, the effect of exercise on MSL in PD tremor dominant patients would hypothetically rely more on the cerebellum and the akinetic-rigid would rely more on mesolimbic-striatal circuit.

5.1.2. Non Motor Symptoms

As previously introduced, a plethora of studies has demonstrated that differences are found at the cognitive and neuropsychiatric levels within PD NMS manifestations. Most recently, studies have been conducted to identify relevant NMS subtyping to provide further understanding of such heterogeneity (Brown et al., 2011; Cholerton et al., 2014; Fereshtehnejad et al., 2015; Goldman, Weis, Stebbins, Bernard et Goetz, 2012; Marras, 2015; Marras et Chaudhuri, 2016). For instance, the notion of mild cognitive impairment (MCI) has been used to describe which and how many cognitive domains are affected (e.g. executive,

visuospatial, memory) and whether it relates to frontal or posterior cognitive functions (Geurtsen et al., 2014; Marras et Chaudhuri, 2016). Furthermore, recent literature reviews on cognitive declines in PD highlight how this deterioration is defined by multiple pathological processes, resulting in great disparity of clinical cognitive manifestations and evolution amongst patients (Lin et Wu, 2015; Monchi et al., 2016). On the one hand, it is established that about 25–40 % of PD individuals develop cognitive dysfunctions in the early stage, which makes them at stakes of developing dementia over the course of the disease. On the other hand, there is still a debate in the literature whether or not separation of groups based purely on cognitive subtyping may provide (or not) sufficient information to determine distinct PD groups (Cholerton et al., 2014; Monchi et al., 2016). At this point, combining cognitive test performance with other factors, such as genetic profile, imaging, biomarkers, and/or motor subtypes is the method used to identify those most likely to rapidly progress to dementia. For example, studies now investigate demographic and clinical features (e.g. neuropsychiatric dysfunction) as it relates to subtypes (most commonly the tremor vs akinetic-rigid subtypes) (Brown et al., 2011). Overall, the akinetic-rigid subtype has consistently been shown to have a broader array of NMS, such as cognitive impairment, anxiety and depression (Marras et Chaudhuri, 2016; Thenganatt et Jankovic, 2014). As such, it would be an interesting avenue to study the effect of treatment, such as AET, in relation to PD cognitive and motor subtypes.

In sum, the PD literature in the last decade has devoted substantial attention to identify subtypes as a mean to demystify the obvious heterogeneous nature of PD. To date, most studies have been conducted on motor symptoms subtyping, and out of these latter, the tremor vs akinetic-rigid subtypes have cumulated the most convincingly evidence of such

distinctive group. Yet, recent efforts have been made and encouraged on including NMS subtyping. At this point, promising NMS subtyping are under investigations and most NMS have been associated with the akinetic-rigid subtypes. While keeping in mind that subtypes are not distinct biological entities (Nutt, 2016), subtyping may help to develop knowledge on the multiple pathological processes of PD as well as to predict the outcome and/or response to treatment in PD, such as AET.

5.2. Perspective on Exercise Diversity

5.2.1. Exercise as a Preventive Measure

By definition, physical activity is defined by any bodily movement produced by skeletal muscles that require an increase over resting energy expenditure. (Després, 2016). As such, exercise is physical activity, but that is planned, structured, and repetitive for the purpose of conditioning any part of the body. Yet, exercise can be based on certain principles, including the frequency, intensity, time and type (FITT), allowing to be more specific in prescribing exercise. Each characteristic brings their unique contribution to improve health, maintain fitness, and is important as a mean for physical rehabilitation. For instance, as a preventive health measure, it is recommended that Canadian adults accumulate at least 150 minutes (time) of moderate- to vigorous-intensity (intensity) aerobic exercise (type) per week (frequency), in bouts of 10 minutes (time) or more as well as perform resistance training (type) at least 2 days per week (frequency) (Reed et Pipe, 2016). Interestingly, numerous health benefits (e.g. risk reductions of premature mortality and alleviation of clinical symptoms for at least 25 different chronic diseases, including PD (Pedersen et Saltin, 2015; Warburton et Bredin, 2016) have been associated with such recommendations. Nevertheless, prescribing

exercise still remains a challenge as each disease has its own mechanism, and the dose-response relationship between physical activity/exercise and various health outcomes is still not well understood. For instance, Warburton et Bredin (2016) reviewed the literature on the dose-response relationship between PA/exercise and various health outcomes. They identified that even half of this standardized recommended volume of physical activity might lead to marked health benefits for certain population living with chronic medical conditions (e.g. diabetes). They concluded that an individualized prescription (dosage) that takes into consideration the unique characteristics and needs of the client is the recommended method to maximize benefits.

Beside the FITT principles, sedentary behaviour is another distinct concept, particularly meaningful to PD's individuals, describing activities (or postures) that require very little movement (e.g. sitting and screen time) (Després, 2016). According to the latter (Després (2016), while a physically active lifestyle is associated with a reduced risk of comorbidities and related mortality, sedentary time has recently emerged as a new risk factor for morbidity and mortality, and this, despite some level of physical activity. Although future studies have to be undertaken to understand at which level sedentary time becomes detrimental to health, the latter highlights the importance of considering the impacts of sedentariness on health. Deteriorating effect of sedentary behaviours might be even more devastating in individuals with chronic disease, such as PD, since the nature of the disease leads to a state of being sedentary.

In sum, to keep a minimum period of sedentary behaviour and to be physically active on a regular basis (ideally, as recommended by world health organisation [WHO] and national

guideline (Tremblay et al., 2011)) is at this point the most evidenced-based and intuitive exercise recommendation for all. However, various health outcomes have to be considered to prescribe exercise as a treatment, such as the dose-response relationship between physical activity/exercise and disease mechanisms. Accordingly, an individualized exercise prescription appears to be the adequate approach.

5.3. Exercise Prescription in Parkinson's Disease Subtypes

Long time ago, Hippocrates suggested that physical activity, performed within reasonable limits, is good for health. This statement seems to apply similarly for individuals with chronic disease, such as PD. To date, recommendations for an individual in the early stage of PD are not much different from the one for a healthy adult. For instance, the American College of Sports Medicine (ACSM) recommends to accumulate a minimum of 150 minutes weekly of physical activity at moderate intensity, including various forms of training such as aerobic, functional, resistance and neuromuscular coordinating-skill training (Moore, 2016). Ideally, individual exercise prescription is encouraged, as PD symptoms vary from one person to another and become more severe in later stages. Moreover, one can speculate that some disease's difficulties may interfere with adherence to physical activity (e.g. motor difficulties, depression, anxiety). In fact, supervised training programs (in a group or individually) have revealed the greatest health gains (e.g. function, balance and gait measures) compared to home-program in PD (King et al., 2015). Overall, exercise as a treatment in PD requires specific considerations on individual's need, knowledge of the disease as well as the dose-response relationship between physical activity/exercise and desired health outcomes. For example, in this thesis, small groups of participants (4) were trained together during the AET program. In

our case, the drop-out level was extremely low, supporting again the idea that a personalised supervised approach was successful. Yet, the exercise program could have been improved by adding complementary exercise, such as resistance and coordination skills. A broader exercise program might have reached various individuals' needs (e.g. neuropsychiatric vs motor symptoms). For instance, different exercise prescription (based on FITT) may, hypothetically, act differently on the brain according to PD subgroups (symptomology). For instance, exercise-dependent plasticity induced by aerobic exercise, explained by the dopaminergic hypothesis (targeting the striatum), may provide a more efficient treatment (at first) for the akinetic-rigid patients (CS involvement in PD dysfunction) than for the PD's tremor subtype (CS and CC involvement in PD dysfunction). Since the PD tremor subtype involves also the CC system, the akinetic-rigid subtype may benefit more quickly from aerobic exercise by targeting the CS dysfunctions directly. However, it is also possible that the tremor subtype benefit more importantly that the akinetic-rigidity group in other type of exercise, such as balance-coordination intervention, as it is one of the functional role of the cerebellum, but it is also an important brain structure that was implicated in exercise dependent plastic change following AET in this present thesis (Stoodley et Schmahmann, 2010). In addition, parameters of exercise such as intensity, frequency and duration may modulate in a distinct fashion the effects of exercise intervention on cognitive functions. To date, many types of exercise (Uhrbrand et al., 2015) have proven to be beneficial in PD, such as AET (Shu et al., 2014) balance-coordination (Wong-Yu et Mak, 2015) and resistance training (Prodoehl et al., 2015). However, the brain mechanisms underlying the effects of exercise are not well understood. For instance, in this thesis project, a three-month at high intensity exercise level was implemented. Hypothetically,

a three-months low/moderate intensity AET program would not have shown same results in this thesis, and maybe it would have taken a six- or twelve-months long program to show similar results at that intensity, as the amount of exercise (months) could have influenced changes within brain activity related to MSL. As such, exercise outcome can also be mediated by the relationship within the FITT principles (e.g. the amount of time/intensity level). Overall, as Uhrbrand et al. (2015) highlighted in reviewing the PD exercise trial literature, intensity level seems important to promote exercise-dependent brain plasticity, but moderate intensity exercise level programs have also shown positive health outcomes. While some benefits are observed after only a short period of acute exercise (Alberts et al., 2016), then how long and how frequent is the right dosage to generate plastic vs compensatory brain changes? And how does it apply for different cognitive functions? Overall, various ambiguities still exist involving exercise parameters to generate health specific outcomes in PD, especially in relation to brain changes.

6. Conclusion

Certainly, over the last decade, the amount of evidence supporting the importance of exercise for optimal health and well-being in PD has grown exponentially ((Hirsch et Farley, 2009b; Hirsch et al., 2016; Roeder et al., 2015; Shu et al., 2014; Zigmond et Smeyne, 2014), for reviews). This collective research has helped shape our understanding of the relationship between exercise and various outcomes in PD. First, an important link has been established between the effect of exercise and improvement of functional capacity and quality of life. Moreover, the exercise and PD literature in mice have allowed to identify important brain mechanisms related to exercise-dependent plasticity, which allow now to speculate on

possible brain mechanisms of such effect in humans. Yet, to use exercise as a treatment, more studies have to be conducted to understand the effect of exercise in PD, especially as it relates to brain structures and functions for motor and non-motor aspects of the disease. This thesis's project responded to the paucity of human brain research by highlighting important functional brain changes (hippocampus, striatum, cerebellum) in relation with MSL and AET. In addition, it investigated the effect of AET in PD on both cognitive and motor functions, which allowed to reflect on the multidimensional nature of PD (motor and NMS), hence representing an ecological point of view of the disease.

Finally, whereas PD is distinct by its heterogeneity, exercise can also be diversified. At first, this global PD and exercise assortment appears as a big puzzle with many pieces to connect. However, with common efforts within the scientific community, the dose-response relationship between exercise and various health outcomes in PD will be understood. At this point, one outcome that remains very important is to investigate the dose-response relationship between exercise and brain functions (e.g. cognition, motor learning) and structural changes (e.g. hippocampus, striatum, cerebellum). Further understanding on the effect of exercise-dependent plasticity and/or compensatory mechanisms in relation to PD heterogeneous symptoms (motor and NMS) is needed, as it may link many pieces of the big puzzle together. Hopefully, this thesis has advanced further this field of research, by putting forward the effect of a progressive intense AET in early PD (3 times a week for 3 months) on both motor learning and cognitive functions. In addition, important brain functions were

identified, and could be involved in plastic and or compensatory mechanisms associated with motor skill learning and AET. Thus, this thesis project supports Hippocrates's philosophy, endorsing that physical activity, performed within reasonable limits, even when you have a chronic disease, such as PD, is great for your health!

References

Aarsland, D., Brønnick, K. et Fladby, T. (2011). Mild Cognitive Impairment in Parkinson's Disease. *Current Neurology and Neuroscience Reports, 11*(4), 371-378.

Abbruzzese, T., Marinelli. (2009). The rational for motor learning in Parkinson's disease. *Eur J Phys Rehabil Med, 45*, 2009-2014.

Ahlskog, J. E. (2011). Does vigorous exercise have a neuroprotective effect in Parkinson disease? *Neurology, 77*(3), 288-294.

Al-Jarrah, M., Jamous, M., Al Zailaey, K. et Bweir, S. O. (2010). Endurance exercise training promotes angiogenesis in the brain of chronic/progressive mouse model of Parkinson's Disease. *NeuroRehabilitation, 26*(4), 369-373.

Alberts, J. L., Linder, S. M., Penko, A. L., Lowe, M. J. et Phillips, M. (2011). It is not about the bike, it is about the pedaling: forced exercise and Parkinson's disease. *Exerc Sport Sci Rev, 39*(4), 177-186. doi: 10.1097/JES.0b013e31822cc71a

Alberts, J. L., Phillips, M., Lowe, M. J., Frankemolle, A., Thota, A., Beall, E. B., . . . Ridgel, A. L. (2016). Cortical and motor responses to acute forced exercise in Parkinson's disease. *Parkinsonism & Related Disorders, 24*, 56-62. doi: http://dx.doi.org/10.1016/j.parkreldis.2016.01.015

Albouy, G., Fogel, S., King, B. R., Laventure, S., Benali, H., Karni, A., . . . Doyon, J. (2015). Maintaining vs. enhancing motor sequence memories: respective roles of striatal and hippocampal systems. *Neuroimage, 108*, 423-434. doi: 10.1016/j.neuroimage.2014.12.049

Albouy, G., King, B. R., Maquet, P. et Doyon, J. (2013). Hippocampus and striatum: dynamics and interaction during acquisition and sleep-related motor sequence memory consolidation. *Hippocampus, 23*(11), 985-1004. doi: 10.1002/hipo.22183

Alzahrani, H. et Venneri, A. (2015). Cognitive and neuroanatomical correlates of neuropsychiatric symptoms in Parkinson's disease: A systematic review. *Journal of the Neurological Sciences, 356*(1–2), 32-44. doi: http://dx.doi.org/10.1016/j.jns.2015.06.037

Amano, S., Roemmich, R. T., Skinner, J. W. et Hass, C. J. (2013). Ambulation and Parkinson disease. *Phys Med Rehabil Clin N Am, 24*(2), 371-392. doi: 10.1016/j.pmr.2012.11.003

Amboni, M., Barone, P. et Hausdorff, J. M. (2013). Cognitive Contributions to Gait and Falls: Evidence and Implications. *Movement disorders : official journal of the Movement Disorder Society, 28*(11), 1520-1533. doi: 10.1002/mds.25674

American College of Sport Medicine (2006). *ACSM's Guidelines for exercise testing and prescription sixth edition*. USA, Philadelphia: Lippincott Williams & Wilkins, Lea & Febiger.

Antonelli, F., Ray, N. et Strafella, A. P. (2010). Imaging cognitive and behavioral symptoms in Parkinson's disease. *Expert Review of Neurotherapeutics, 10*(12), 1827-1838.

Audiffren, M., André, N. et Albinet, C. (2011). Effets positifs de l'exercice physique chronique sur les fonctions cognitives des seniors: bilan et perspectives. *Revue de neuropsychologie neurosciences cognitives et cliniques, 3*(4), 207-225.

Ballesteros, S., Kraft, E., Santana, S. et Tziraki, C. (2015). Maintaining older brain functionality: A targeted review. *Neuroscience & Biobehavioral Reviews, 55*, 453-477. doi: http://dx.doi.org/10.1016/j.neubiorev.2015.06.008

Barker, R. A. et Williams-Gray, C. H. (2014). Mild cognitive impairment and Parkinson's disease-Something to remember. *Journal of Parkinson's Disease, 4*(4), 651-656. doi: 10.3233/JPD-140427

Bartholomew, J., Ciccolo, J., Spirduso, W., Poon, L. et Chodzo-Zajko, W. (2008). *Exercise, depression, and cognition," in Exercise and Its Mediating Effects on Cognition*.

Bauman, A., Merom, D., Bull, F. C., Buchner, D. M. et Fiatarone Singh, M. A. (2016). Updating the Evidence for Physical Activity: Summative Reviews of the Epidemiological Evidence, Prevalence, and Interventions to Promote "Active Aging". *The Gerontologist, 56*(Suppl 2), S268-S280. doi: 10.1093/geront/gnw031

Beall, E. B., Lowe, M. J., Alberts, J. L., Frankemolle, A. M. M., Thota, A. K., Shah, C. et Phillips, M. D. (2013). The Effect of Forced-Exercise Therapy for Parkinson's Disease on Motor Cortex Functional Connectivity. *Brain Connectivity, 3*(2), 190-198. doi: 10.1089/brain.2012.0104

Beaudreau, S. A. et O'Hara, R. (2009). The Association of Anxiety and Depressive Symptoms with Cognitive Performance in Community-Dwelling Older Adults. *Psychology and Aging, 24*(2), 507-512. doi: 10.1037/a0016035

Beck, A. T. et Beamesderfer, A. (1974). Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry, 7*(0), 151-169.

Bédard, P. et Sanes, J. N. (2009). On a basal ganglia role in learning and rehearsing visual–motor associations. *NeuroImage, 47*(4), 1701-1710. doi: 10.1016/j.neuroimage.2009.03.050

Bennett, I. J., Madden, D. J., Vaidya, C. J., Howard Jr, J. H. et Howard, D. V. White matter integrity correlates of implicit sequence learning in healthy aging. *Neurobiology of Aging, In Press, Corrected Proof*.

Bertram, S., Brixius, K. et Brinkmann, C. (2016). Exercise for the diabetic brain: how physical training may help prevent dementia and Alzheimer's disease in T2DM patients. *Endocrine*, 1-14. doi: 10.1007/s12020-016-0976-8

Beyer, M. K., Janvin, C. C., Larsen, J. P. et Aarsland, D. (2007). A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. *Journal of Neurology, Neurosurgery & Psychiatry, 78*(3), 254-259.

Bherer, L. (2015). Cognitive plasticity in older adults: effects of cognitive training and physical exercise. *Annals of the New York Academy of Sciences, 1337*(1), 1-6. doi: 10.1111/nyas.12682

Bherer, L., Erickson, K. I. et Liu-Ambrose, T. (2013a). Physical exercise and brain functions in older adults. *J Aging Res, 2013*, 197326. doi: 10.1155/2013/197326

Bherer, L., Erickson, K. I. et Liu-Ambrose, T. (2013b). A Review of the Effects of Physical Activity and Exercise on Cognitive and Brain Functions in Older Adults. *J Aging Res, 2013*, 657508. doi: 10.1155/2013/657508

Borg, G. (1982). Psychophysical bases of perceived exertion. *Med Sci Sports Exerc. , 14*, 377–381.

Bostan, A. C. et Strick, P. L. (2010a). The Cerebellum and Basal Ganglia are Interconnected. *Neuropsychology Review, 20*(3), 261-270. doi: 10.1007/s11065-010-9143-9

Bostan, A. C. et Strick, P. L. (2010b). The cerebellum and basal ganglia are interconnected. *Neuropsychol Rev, 20*(3), 261-270.

Braak, H., Rub, U. et Braak, E. (2000). [Neuroanatomy of Parkinson disease. Changes in the neuronal cytoskeleton of a few disease-susceptible types of neurons lead to progressive destruction of circumscribed areas in the limbic and motor systems]. *Nervenarzt, 71*(6), 459-469.

Braak, H., Rüb, U. et Del Tredici, K. (2006). Cognitive decline correlates with neuropathological stage in Parkinson's disease. *Journal of the Neurological Sciences, 248*(1-2), 255-258.

Braak, H., Tredici, K. D., Rüb, U., de Vos, R. A. I., Jansen Steur, E. N. H. et Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging, 24*(2), 197-211.

Brown, R. G., Landau, S., Hindle, J. V., Playfer, J., Samuel, M., Wilson, K. C., . . . Group, f. t. P.-P. S. (2011). Depression and anxiety related subtypes in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 82*(7), 803-809. doi: 10.1136/jnnp.2010.213652

Calabresi, P., Castrioto, A., Di Filippo, M. et Picconi, B. (2013). New experimental and clinical links between the hippocampus and the dopaminergic system in Parkinson's disease. *Lancet Neurol, 12*(8), 811-821. doi: 10.1016/S1474-4422(13)70118-2

Canadian Society for Exercise Physiology (1996). *Professional Fitness Lifestyle Consultant 2. Reference Manual*. Ottawa.

Carbon, M. et Eidelberg, D. (2006). Functional imaging of sequence learning in Parkinson's disease. *J Neurol Sci, 248*(1-2), 72-77.

Carbon, M., Reetz, K., Ghilardi, M. F., Dhawan, V. et Eidelberg, D. (2010). Early Parkinson's disease: longitudinal changes in brain activity during sequence learning. *Neurobiol Dis, 37*(2), 455-460.

Chen, H.-M., Wang, Z.-J., Fang, J.-P., Gao, L.-Y., Ma, L.-Y., Wu, T., . . . Feng, T. (2015). Different Patterns of Spontaneous Brain Activity between Tremor-Dominant and Postural Instability/Gait Difficulty Subtypes of Parkinson's Disease: A Resting-State fMRI Study. *CNS Neuroscience & Therapeutics, 21*(10), 855-866. doi: 10.1111/cns.12464

Chen, H., Zhang, S. M., Schwarzschild, M. A., Hernan, M. A. et Ascherio, A. (2005). Physical activity and the risk of Parkinson disease. *Neurology, 64*(4), 664-669.

Cholerton, B. A., Zabetian, C. P., Wan, J. Y., Montine, T. J., Quinn, J. F., Mata, I. F., . . . Edwards, K. L. (2014). Evaluation of Mild Cognitive Impairment Subtypes in Parkinson's Disease. *Movement disorders : official journal of the Movement Disorder Society, 29*(6), 756-764. doi: 10.1002/mds.25875

Christopher, L. et Strafella, A. P. (2013). Neuroimaging of brain changes associated with cognitive impairment in Parkinson's disease. *J Neuropsychol*. doi: 10.1111/jnp.12015

Clark, G., Lum, J. et Ullman, M. (2014). A meta-analysis and meta-regression of serial reaction time tast performance in Parkinson's disease. *Neuropsychology*.

Clark, G. M., Lum, J. A. G. , and Ullman, M. T. . (2014). A meta-analysis and meta-regression of serial reaction time tast performance in Parkinson's disease. *Neuropsychology*.

Clegg, B. A., DiGirolamo, G. J. et Keele, S. W. (1998). Sequence learning. *Trends in Cognitive Sciences, 2*(8), 275-281. doi: 10.1016/s1364-6613(98)01202-9

Colcombe, S. et Kramer, A. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci, 14*, 125 - 130.

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E. et Kramer, A. F. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci, 58*(2), 176-180.

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., . . . Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci, 61*(11), 1166-1170.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., . . . Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A, 101*(9), 3316-3321.

Coles, K. et Tomporowski, P. D. (2008). Effects of acute exercise on executive processing, short-term and long-term memory. *J Sports Sci, 26*(3), 333-344.

Cools, R., Barker, R. A., Sahakian, B. J. et Robbins, T. W. (2001). Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain, 124*(12), 2503-2512.
Cronin-Golomb, A. (2013). Emergence of Nonmotor Symptoms as the Focus of Research and Treatment of Parkinson's Disease: Introduction to the Special Section on Nonmotor Dysfunctions in Parkinson's Disease. *Behavioral neuroscience, 127*(2), 135-138. doi: 10.1037/a0032142
Cruise, K. E., Bucks, R. S., Loftus, A. M., Newton, R. U., Pegoraro, R. et Thomas, M. G. (2011). Exercise and Parkinson's: benefits for cognition and quality of life. *Acta Neurol Scand, 123*(1), 13-19. doi: 10.1111/j.1600-0404.2010.01338.x
Curran, T. (1997). Higher-order associative learning in amnesia: Evidence from the serial reaction time task. *Journal of Cognitive Neuroscience, 9*(522-533).
Dan, X., King, B. R., Doyon, J. et Chan, P. (2015). Motor Sequence Learning and Consolidation in Unilateral De Novo Patients with Parkinson's Disease. *PLoS One, 10*(7), e0134291. doi: 10.1371/journal.pone.0134291
de la Riva, P., Smith, K., Xie, S. X. et Weintraub, D. (2014). Course of psychiatric symptoms and global cognition in early Parkinson disease. *Neurology, 83*(12), 1096-1103. doi: 10.1212/WNL.0000000000000801
Del Tredici, K. et Braak, H. (2016). Review: Sporadic Parkinson's disease: development and distribution of α-synuclein pathology. *Neuropathology and Applied Neurobiology, 42*(1), 33-50. doi: 10.1111/nan.12298
Després, J.-P. (2016). Physical Activity, Sedentary Behaviours, and Cardiovascular Health: When Will Cardiorespiratory Fitness Become a Vital Sign? *Canadian Journal of Cardiology, 32*(4), 505-513. doi: http://dx.doi.org/10.1016/j.cjca.2015.12.006
Destrebecqz, A. et Cleeremans, A. (2001). Can sequence learning be implicit? New evidence with the process dissociation procedure. *Psychon Bull Rev, 8*(2), 343-350.
Destrebecqz, A. C., A. . (2001). Can sequence learning be implicit? New evidence with the Process Dissociation Procedure. *Psychonomic Bulletin & Review, 8*(2), 343-350.
Dietrich, A. et Audiffren, M. (2011). The reticular-activating hypofrontality (RAH) model of acute exercise. *Neurosci Biobehav Rev, 35*(6), 1305-1325.
Dirnberger, G. et Jahanshahi, M. (2013). Executive dysfunction in Parkinson's disease: a review. *J Neuropsychol, 7*(2), 193-224. doi: 10.1111/jnp.12028
Dishman, R. K. (2006). The new emergence of exercise neurobiology. *Scand J Med Sci Sports, 16*(6), 379-380.
Dishman, R. K., Berthoud, H. R., Booth, F. W., Cotman, C. W., Edgerton, V. R., Fleshner, M. R., . . . Zigmond, M. J. (2006). Neurobiology of exercise. *Obesity (Silver Spring), 14*(3), 345-356.
Djaldetti, R., Ziv, I. et Melamed, E. (2006). The mystery of motor asymmetry in Parkinson's disease. *Lancet Neurol, 5*(9), 796-802.
Doyon, J. (2008). Motor sequence learning and movement disorders. *Curr Opin Neurol, 21*(4), 478-483.
Doyon, J., Bellec, P., Amsel, R., Penhune, V., Monchi, O., Carrier, J., . . . Benali, H. (2009). Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav Brain Res, 199*(1), 61-75.
Doyon, J. et Benali, H. (2005a). Reorganization and plasticity in the adult brain during learning of motor skills. *Curr Opin Neurobiol, 15*(2), 161-167. doi: 10.1016/j.conb.2005.03.004
Doyon, J. et Benali, H. (2005b). Reorganization and plasticity in the adult brain during learning of motor skills. *Current Opinion in Neurobiology, 15*(2), 161-167.

Doyon, J., Orban, P., Barakat, M., Debas, K., Lungu, O., Albouy, G., . . . Benali, H. (2011a). [Functional brain plasticity associated with motor learning.]. *Med Sci (Paris), 27*(4), 413-420.

Doyon, J., Orban, P., Barakat, M., Debas, K., Lungu, O., Albouy, G., . . . Benali, H. (2011b). [Functional brain plasticity associated with motor learning]. *Med Sci (Paris), 27*(4), 413-420. doi: 10.1051/medsci/2011274018

Doyon, J., Penhune, V. et Ungerleider, L. G. (2003). Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia, 41*(3), 252-262.

Doyon, J., Song, A. W., Karni, A., Lalonde, F., Adams, M. M. et Ungerleider, L. G. (2002). Experience-dependent changes in cerebellar contributions to motor sequence learning. *Proc Natl Acad Sci U S A, 99*(2), 1017-1022. doi: 10.1073/pnas.022615199

Duchesne, C., Lungu, O., Nadeau, A., Robillard, M. E., Bore, A., Bobeuf, F., . . . Doyon, J. (2015). Enhancing both motor and cognitive functioning in Parkinson's disease: Aerobic exercise as a rehabilitative intervention. *Brain Cogn, 99*, 68-77. doi: 10.1016/j.bandc.2015.07.005

Duzel, E., van Praag, H. et Sendtner, M. (2016). Can physical exercise in old age improve memory and hippocampal function? *Brain, 139*(3), 662-673. doi: 10.1093/brain/awv407

Eckert, T. et Eidelberg, D. (2005). Neuroimaging and therapeutics in movement disorders. *NeuroRx, 2*(2), 361-371.

Eckert, T., Tang, C. et Eidelberg, D. (2007). Assessment of the progression of Parkinson's disease: a metabolic network approach. *Lancet Neurol, 6*(10), 926-932.

Eidelberg, D., Moeller, J. R., Dhawan, V., Sidtis, J. J., Ginos, J. Z., Strother, S. C., . . . Rottenberg, D. A. (1990). The metabolic anatomy of Parkinson's disease: complementary [18F]fluorodeoxyglucose and [18F]fluorodopa positron emission tomographic studies. *Mov Disord, 5*(3), 203-213.

Eime, R. M., Young, J. A., Harvey, J. T., Charity, M. J. et Payne, W. R. (2013). A systematic review of the psychological and social benefits of participation in sport for adults: informing development of a conceptual model of health through sport. *International Journal of Behavioral Nutrition and Physical Activity, 10*(1), 1-14. doi: 10.1186/1479-5868-10-135

Elgh, E., Domellöf, M., Linder, J., Edström, M., Stenlund, H. et Forsgren, L. (2009). Cognitive function in early Parkinson's disease: a population-based study. *European Journal of Neurology, 16*(12), 1278-1284.

Ellis, T., Cavanaugh, J. T., Earhart, G. M., Ford, M. P., Foreman, K. B., Fredman, L., . . . Dibble, L. E. (2011). Factors Associated With Exercise Behavior in People With Parkinson Disease. *Physical Therapy, 91*(12), 1838-1848. doi: 10.2522/ptj.20100390

Erickson, K. I., Leckie, R. L. et Weinstein, A. M. (2014). Physical activity, fitness, and gray matter volume. *Neurobiology of Aging, 35, Supplement 2*, S20-S28. doi: http://dx.doi.org/10.1016/j.neurobiolaging.2014.03.034

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A, 108*(7), 3017-3022. doi: 10.1073/pnas.1015950108

Fabel, K. et Kempermann, G. (2008). Physical Activity and the Regulation of Neurogenesis in the Adult and Aging Brain. *NeuroMolecular Medicine, 10*(2), 59-66.

Fama, R. et Sullivan, E. V. (2002). Motor sequencing in Parkinson's disease: relationship to executive function and motor rigidity. *Cortex, 38*(5), 753-767.

Fereshtehnejad, S. M., Romenets, S. R., Anang, J. B., Latreille, V., Gagnon, J. F. et Postuma, R. B. (2015). New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort Comparison With Other Phenotypes. *JAMA Neurol, 72*(8), 863-873. doi: 10.1001/jamaneurol.2015.0703

Fisher, B. E., Li, Q., Nacca, A., Salem, G. J., Song, J., Yip, J., . . . Petzinger, G. M. (2013). Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. *NeuroReport, 24*(10), 509-514. doi: 10.1097/WNR.0b013e328361dc13

Fisher, B. E., Petzinger, G. M., Nixon, K., Hogg, E., Bremmer, S., Meshul, C. K. et Jakowec, M. W. (2004). Exercise-induced behavioral recovery and neuroplasticity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse basal ganglia. *J Neurosci Res, 77*(3), 378-390.

Fisher, B. E., Wu, A. D., Salem, G. J., Song, J., Lin, C. H., Yip, J., . . . Petzinger, G. (2008). The effect of exercise training in improving motor performance and corticomotor excitability in people with early Parkinson's disease. *Arch Phys Med Rehabil, 89*(7), 1221-1229.

Folstein, M., Folstein, S. et McHugh, P. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*, 189 - 198.

Gamble, K. R., Cummings, T. J., Jr., Lo, S. E., Ghosh, P. T., Howard, J. H., Jr. et Howard, D. V. (2014). Implicit sequence learning in people with Parkinson's disease. *Front Hum Neurosci, 8*, 563. doi: 10.3389/fnhum.2014.00563

Geurtsen, G. J., Hoogland, J., Goldman, J. G., Schmand, B. A., Tröster, A. I., Burn, D. J. et Litvan, I. (2014). Parkinson's Disease Mild Cognitive Impairment: Application and Validation of the Criteria. *Journal of Parkinson's disease, 4*(2), 131-137. doi: 10.3233/JPD-130304

Gillian M. Clark, J. A. G. L., and Michael T. Ullman. (2014). A meta-analysis and meta-regression of serial reaction time tast performance in Parkinson's disease. *Neuropsychology*.

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., . . . LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders, 23*(15), 2129-2170. doi: 10.1002/mds.22340

Goldman, J. G. et Postuma, R. (2014). Premotor and nonmotor features of Parkinson's disease. *Current Opinion in Neurology, 27*(4), 434-441. doi: 10.1097/wco.0000000000000112

Goldman, J. G., Weis, H., Stebbins, G., Bernard, B. et Goetz, C. G. (2012). Clinical differences among mild cognitive impairment subtypes in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society, 27*(9), 1129-1136. doi: 10.1002/mds.25062

Gomez-Pinilla, F., Zhuang, Y., Feng, J., Ying, Z. et Fan, G. (2011). Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *European Journal of Neuroscience, 33*(3), 383-390.

Goodwin, V. A., Richards, S. H., Taylor, R. S., Taylor, A. H. et Campbell, J. L. (2008). The effectiveness of exercise interventions for people with Parkinson's disease: a systematic review and meta-analysis. *Mov Disord, 23*(5), 631-640.

Gordon, B. A., Rykhlevskaia, E. I., Brumback, C. R., Lee, Y., Elavsky, S., Konopack, J. F., . . . Fabiani, M. (2008). Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. *Psychophysiology, 45*(5), 825-838.

Gracies, J. M. (2010). [Neurorehabilitation in parkinsonian syndromes]. *Rev Neurol (Paris), 166*(2), 196-212.

Gregory, M. A., Gill, D. P. et Petrella, R. J. (2013). Brain Health and Exercise in Older Adults. *Current Sports Medicine Reports, 12*(4), 256-271. doi: 10.1249/JSR.0b013e31829a74fd

Hasan, S. M. M., Rancourt, S. N., Austin, M. W. et Ploughman, M. (2016). Defining Optimal Aerobic Exercise Parameters to Affect Complex Motor and Cognitive Outcomes after Stroke: A Systematic Review and Synthesis. *Neural Plasticity, 2016*, 12. doi: 10.1155/2016/2961573

Hayes, W. M., Fung, S. V., Kimber, E. T. et O'Sullivan, D. J. (2010). Current concepts in the management of Parkinson disease. *The Medical Journal of Australia, 192*(3), 144-149.

Herman, T., Giladi, N., Gruendlinger, L. et Hausdorff, J. M. (2007). Six weeks of intensive treadmill training improves gait and quality of life in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil, 88*(9), 1154-1158.

Herman, T., Giladi, N. et Hausdorff, J. M. (2009). Treadmill training for the treatment of gait disturbances in people with Parkinson's disease: a mini-review. *J Neural Transm, 116*(3), 307-318.

Hillman, C. H., Erickson, K. I. et Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci, 9*(1), 58-65.

Hillman, C. H., Kamijo, K. et Scudder, M. (2011). A review of chronic and acute physical activity participation on neuroelectric measures of brain health and cognition during childhood. *Prev Med*.

Hillman, C. H., Pontifex, M. B., Raine, L. B., Castelli, D. M., Hall, E. E. et Kramer, A. F. (2009). The effect of acute treadmill walking on cognitive control and academic achievement in preadolescent children. *Neuroscience, 159*(3), 1044-1054.

Hillman, C. H., Snook, E. M. et Jerome, G. J. (2003). Acute cardiovascular exercise and executive control function. *Int J Psychophysiol, 48*(3), 307-314.

Hirano, S., Shinotoh, H. et Eidelberg, D. (2012). Functional brain imaging of cognitive dysfunction in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 83*(10), 963-969. doi: 10.1136/jnnp-2011-301818

Hirsch, M. et Farley, B. (2009a). Exercise and neuroplasticity in persons living with Parkinson's disease. *Eur J Phys Rehabil Med, 45*, 215 - 229.

Hirsch, M. A. et Farley, B. G. (2009b). Exercise and neuroplasticity in persons living with Parkinson's disease. *Eur J Phys Rehabil Med, 45*(2), 215-229.

Hirsch, M. A., Iyer, S. S. et Sanjak, M. (2016). Exercise-induced neuroplasticity in human Parkinson's disease: What is the evidence telling us? *Parkinsonism & Related Disorders, 22, Supplement 1*, S78-S81. doi: http://dx.doi.org/10.1016/j.parkreldis.2015.09.030

Hoehn, M. M. et Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology, 17*(5), 427-442.

Holschneider, D. P., Yang, J., Guo, Y. et Maarek, J. M. (2007). Reorganization of functional brain maps after exercise training: Importance of cerebellar-thalamic-cortical pathway. *Brain Res, 1184*, 96-107. doi: 10.1016/j.brainres.2007.09.081

Hoshi, E., Tremblay, L., Feger, J., Carras, P. L. et Strick, P. L. (2005). The cerebellum communicates with the basal ganglia. *Nat Neurosci, 8*(11), 1491-1493. doi: http://www.nature.com/neuro/journal/v8/n11/suppinfo/nn1544_S1.html

Huang, P., Fang, R., Li, B. et Chen, S.-d. (2016). Exercise-related changes of networks in aging and mild cognitive impairment brain. *Frontiers in Aging Neuroscience, 8*. doi: 10.3389/fnagi.2016.00047

Huang, T. Y., Lin, L. S., Cho, K. C., Chen, S. J., Kuo, Y. M., Wu, F. S., . . . Jen, C. J. (2012). Chonic treadmill exercise in rats delicately alters the Purkinje cell structure to improve motor performance and toxin-resistance in the cerebellum. *J. Appl Physiol*.

Ibarretxe-Bilbao, N., Tolosa, E., Junque, C. et Marti, M.-J. (2009). MRI and cognitive impairment in Parkinson's disease. *Movement Disorders, 24*(S2), S748-S753.

Jackson, A. S., Blair, S. N., Mahar, M. T., L.T., W., Ross, R. M. et Stuteville, J. E. (1990). Prediction of functional aerobic capacity without exercise testing. *Medicine & Science in Sports & Exercise, 22*(6), 863-870.

Janvin, C. C., Larsen, J. P., Aarsland, D. et Hugdahl, K. (2006). Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord, 21*(9), 1343-1349.

Janvin, C. C., Larsen, J. P., Salmon, D. P., Galasko, D., Hugdahl, K. et Aarsland, D. (2006). Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with dementia with lewy bodies and Alzheimer's disease. *Mov Disord, 21*(3), 337-342.

Jellinger, K. A. (2012). Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. *Mov Disord, 27*(1), 8-30. doi: 10.1002/mds.23795

Johnco, C., Wuthrich, V. M. et Rapee, R. M. (2015). THE IMPACT OF LATE-LIFE ANXIETY AND DEPRESSION ON COGNITIVE FLEXIBILITY AND COGNITIVE RESTRUCTURING SKILL ACQUISITION. *Depression and Anxiety*, n/a-n/a. doi: 10.1002/da.22375

Kaltsatou, A., Grigoriou, S. S., Karatzaferi, C., Giannaki, C. D., Stefanidis, I. et Sakkas, G. K. (2015). Cognitive function and exercise training for chronic renal disease patients: A literature review. *Journal of Bodywork and Movement Therapies, 19*(3), 509-515. doi: http://dx.doi.org/10.1016/j.jbmt.2015.04.006

King, B. R., Fogel, S. M., Albouy, G. et Doyon, J. (2013). Neural correlates of the age-related changes in motor sequence learning and motor adaptation in older adults. *Front Hum Neurosci, 7*, 142. doi: 10.3389/fnhum.2013.00142

King, L. A., Wilhelm, J., Chen, Y., Blehm, R., Nutt, J., Chen, Z., . . . Horak, F. B. (2015). Effects of Group, Individual, and Home Exercise in Persons With Parkinson Disease: A Randomized Clinical Trial. *Journal of Neurologic Physical Therapy, 39*(4), 204-212. doi: 10.1097/npt.0000000000000101

Kirk-Sanchez, N. J. et McGough, E. L. (2014). Physical exercise and cognitive performance in the elderly: current perspectives. *Clinical Interventions in Aging, 9*, 51-62. doi: 10.2147/CIA.S39506

Kleemeyer, M. M., Kühn, S., Prindle, J., Bodammer, N. C., Brechtel, L., Garthe, A., . . . Lindenberger, U. (2016). Changes in fitness are associated with changes in hippocampal microstructure and hippocampal volume among older adults. *NeuroImage, 131*, 155-161. doi: http://dx.doi.org/10.1016/j.neuroimage.2015.11.026

Kramer, A. F., Erickson, K. I. et Colcombe, S. J. (2006). Exercise, cognition, and the aging brain. *J Appl Physiol, 101*(4), 1237-1242.

Kudlicka, A., Clare, L. et Hindle, J. V. (2011). Executive functions in Parkinson's disease: Systematic review and meta-analysis. *Movement Disorders, 26*(13), 2305-2315. doi: 10.1002/mds.23868

Langlois, F., Vu, T. T., Chasse, K., Dupuis, G., Kergoat, M. J. et Bherer, L. (2012). Benefits of Physical Exercise Training on Cognition and Quality of Life in Frail Older Adults. *J Gerontol B Psychol Sci Soc Sci*. doi: 10.1093/geronb/gbs069

Langlois, F., Vu, T. T., Chasse, K., Dupuis, G., Kergoat, M. J. et Bherer, L. (2013). Benefits of physical exercise training on cognition and quality of life in frail older adults. *J Gerontol B Psychol Sci Soc Sci, 68*(3), 400-404. doi: 10.1093/geronb/gbs069

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P. et Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med, 144*(2), 73-81.

Lau, Y.-S., Patki, G., Das-Panja, K., Le, W.-D. et Ahmad, S. O. (2011). Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson's disease with moderate neurodegeneration. *European Journal of Neuroscience, 33*(7), 1264-1274.

Lee, H. M. et Koh, S.-B. (2015). Many Faces of Parkinson's Disease: Non-Motor Symptoms of Parkinson's Disease. *JMD, 8*(2), 92-97. doi: 10.14802/jmd.15003

Leggio, M. et Molinari, M. (2015). Cerebellar Sequencing: a Trick for Predicting the Future. *The Cerebellum, 14*(1), 35-38. doi: 10.1007/s12311-014-0616-x

Lewis, M. M., Du, G., Sen, S., Kawaguchi, A., Truong, Y., Lee, S., . . . Huang, X. (2011). Differential involvement of striato- and cerebello-thalamo-cortical pathways in tremor- and akinetic/rigid-predominant Parkinson's disease. *Neuroscience, 177*, 230-239.

Lewis, M. M., Galley, S., Johnson, S., Stevenson, J., Huang, X. et McKeown, M. J. (2013). The Role of the Cerebellum in the Pathophysiology of Parkinson's Disease. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques, 40*(03), 299-306. doi: doi:10.1017/S0317167100014232

Lin, C.-H. et Wu, R.-M. (2015). Biomarkers of cognitive decline in Parkinson's disease. *Parkinsonism & Related Disorders, 21*(5), 431-443. doi: http://dx.doi.org/10.1016/j.parkreldis.2015.02.010

Lindsay, J., Laurin, D., Verreault, R., Hebert, R., Helliwell, B., Hill, G. B. et McDowell, I. (2002). Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol, 156*(5), 445-453.

Liu-Ambrose, T. et Donaldson, M. G. (2009). Exercise and cognition in older adults: is there a role for resistance training programmes? *British Journal of Sports Medicine, 43*(1), 25-27. doi: 10.1136/bjsm.2008.055616

Liu-Ambrose, T., Eng, J., Boyd, L., Jacova, C., Davis, J., Bryan, S., . . . Hsiung, G.-Y. (2010). Promotion of the mind through exercise (PROMoTE): a proof-of-concept randomized controlled trial of aerobic exercise training in older adults with vascular cognitive impairment. *BMC Neurology, 10*(1), 14.

Liu-Ambrose, T., Nagamatsu, L. S., Graf, P., Beattie, B. L., Ashe, M. C. et Handy, T. C. (2010). Resistance training and executive functions: a 12-month randomized controlled trial. *Arch Intern Med, 170*(2), 170-178. doi: 10.1001/archinternmed.2009.494

Maass, A., Düzel, S., Brigadski, T., Goerke, M., Becke, A., Sobieray, U., . . . Düzel, E. (2016). Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. *NeuroImage, 131*, 142-154. doi: http://dx.doi.org/10.1016/j.neuroimage.2015.10.084

Mailey, E. L., White, S. M., Wojcicki, T. R., Szabo, A. N., Kramer, A. F. et McAuley, E. (2010). Construct validation of a non-exercise measure of cardiorespiratory fitness in older adults. *BMC Public Health, 10*, 59.

Mang, C. S., Snow, N. J., Campbell, K. L., Ross, C. J. et Boyd, L. A. (2014). A single bout of high-intensity aerobic exercise facilitates response to paired associative stimulation and promotes sequence-specific implicit motor learning. *J Appl Physiol (1985), 117*(11), 1325-1336. doi: 10.1152/japplphysiol.00498.2014

Marinus, J., Verbaan, D. et van Hilten, J. J. (2011). The MoCA: well-suited screen for cognitive impairment in Parkinson disease. *Neurology, 76*(22), 1944; author reply 1944-1945. doi: 10.1212/WNL.0b013e318219dc77

Marras, C. (2015). Subtypes of Parkinson's disease: state of the field and future directions. *Current Opinion in Neurology, 28*(4), 382-386.

Marras, C. et Chaudhuri, K. R. (2016). Nonmotor features of Parkinson's disease subtypes. *Movement Disorders*, n/a-n/a. doi: 10.1002/mds.26510

Marsh, C. E. (2012). Evaluation of the American College of Sports Medicine Submaximal Treadmill Running Test for Predicting V̇o2max. *The Journal of Strength & Conditioning Research, 26*(2), 548-554. doi: 10.1519/JSC.0b013e318220d9a8

Martinu, K. et Monchi, O. (2013). Cortico-basal ganglia and cortico-cerebellar circuits in Parkinson's disease: Pathophysiology or compensation? *Behavioral Neuroscience, 127*(2), 222-236. doi: 10.1037/a0031226

McAuley, E., Elavsky, S., Spirduso, W., Poon, L. et Chodzo-Zajko, W. (2008). *Self-efficacy, physical activity, and cognitive function," in Exercise and Its Mediating Effects on Cognition*.

McAuley, E., Szabo, A. N., Mailey, E. L., Erickson, K. I., Voss, M., White, S. M., . . . Kramer, A. F. (2011). Non-Exercise Estimated Cardiorespiratory Fitness: Associations with Brain Structure, Cognition, and Memory Complaints in Older Adults. *Ment Health Phys Act, 4*(1), 5-11.

McAuley, E., Szabo, A. N., Mailey, E. L., Erickson, K. I., Voss, M., White, S. M., . . . Kramer, A. F. (2011). Non-exercise estimated cardiorespiratory fitness: Associations with brain structure, cognition, and memory complaints in older adults. *Mental Health and Physical Activity, 4*(1), 5-11.

McKee, K. E. et Hackney, M. E. (2013). The effects of adapted tango on spatial cognition and disease severity in Parkinson's disease. *J Mot Behav, 45*(6), 519-529. doi: 10.1080/00222895.2013.834288

Mentis, M. J., Dhawan, V., Nakamura, T., Ghilardi, M. F., Feigin, A., Edwards, C., . . . Eidelberg, D. (2003). Enhancement of brain activation during trial-and-error sequence learning in early PD. *Neurology, 60*(4), 612-619.

Monchi, O., Hanganu, A. et Bellec, P. (2016). Markers of cognitive decline in PD: The case for heterogeneity. *Parkinsonism & Related Disorders, 24*, 8-14. doi: http://dx.doi.org/10.1016/j.parkreldis.2016.01.002

Monchi, O., Petrides, M., Doyon, J., Postuma, R. B., Worsley, K. et Dagher, A. (2004). Neural bases of set-shifting deficits in Parkinson's disease. *J Neurosci, 24*(3), 702-710.

Monchi, O., Petrides, M., Mejia-Constain, B. et Strafella, A. P. (2007). Cortical activity in Parkinson's disease during executive processing depends on striatal involvement. *Brain, 130*(Pt 1), 233-244. doi: 10.1093/brain/awl326

Monteiro, E. P., Franzoni, L. T., Cubillos, D. M., de Oliveira Fagundes, A., Carvalho, A. R., Oliveira, H. B., . . . Peyré-Tartaruga, L. A. (2016). Effects of Nordic walking training on functional parameters in Parkinson's disease: a randomized controlled clinical trial. *Scandinavian Journal of Medicine & Science in Sports*, n/a-n/a. doi: 10.1111/sms.12652

Moore, E. G., Durstine, J. Larry, Painter, L. Patricia (2016). ACSM's Exercise Management for Persons With Chronic Diseases and Disabilities. (4th Edition).

Motl, R. W. et Sandroff, B. M. (2015). Benefits of Exercise Training in Multiple Sclerosis. *Current Neurology and Neuroscience Reports, 15*(9), 1-9. doi: 10.1007/s11910-015-0585-6

Murray, D. K., Sacheli, M. A., Eng, J. J. et Stoessl, A. J. (2014). The effects of exercise on cognition in Parkinson's disease: a systematic review. *Transl Neurodegener, 3*(1), 2047-9158.

Muslimovic, D., Post, B., Speelman, J. D., De Haan, R. J. et Schmand, B. (2009). Cognitive decline in Parkinson's disease: A prospective longitudinal study. *Journal of the International Neuropsychological Society, 15*(03), 426-437.

Muslimović, D., Post, B., Speelman, J. D. et Schmand, B. (2007). Motor procedural learning in Parkinson's disease. *Brain, 130*(11), 2887-2897.

Mustroph, M. L., Chen, S., Desai, S. C., Cay, E. B., DeYoung, E. K. et Rhodes, J. S. (2012). Aerobic exercise is the critical variable in an enriched environment that increases hippocampal neurogenesis and water maze learning in male C57BL/6J mice. *Neuroscience, 219*, 62-71. doi: 10.1016/j.neuroscience.2012.06.007

Nadeau, A., Pourcher, E. et Corbeil, P. (2014). Effects of 24 wk of Treadmill Training on Gait Performance in Parkinson's Disease. *Medicine & Science in Sports & Exercise, 46*(4), 645-655 610.1249/MSS.0000000000000144.

Nazem, S., Siderowf, A. D., Duda, J. E., Ten Have, T., Colcher, A., Horn, S. S., . . . Weintraub, D. (2009). Montreal Cognitive Assessment Performance in Patients with Parkinson's Disease with

"Normal" Global Cognition According to Mini-Mental State Examination Score. *Journal of the American Geriatrics Society, 57*(2), 304-308. doi: 10.1111/j.1532-5415.2008.02096.x

Nissen et Bullemer. (1987a). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology 19*(1), 32.

Nissen, M. J. et Bullemer, P. (1987b). Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology, 19*(1), 1-32.

Nutt, J. G. (2016). Motor subtype in Parkinson's disease: Different disorders or different stages of disease? *Movement Disorders*, n/a-n/a. doi: 10.1002/mds.26657

Obeso, I., Wilkinson, L., Casabona, E., Bringas, M., Álvarez, M., Álvarez, L., . . . Jahanshahi, M. (2011). Deficits in inhibitory control and conflict resolution on cognitive and motor tasks in Parkinson's disease. *Experimental Brain Research, 212*(3), 371-384. doi: 10.1007/s00221-011-2736-6

Obeso, J. A., Rodríguez-Oroz, M. C., Benitez-Temino, B., Blesa, F. J., Guridi, J., Marin, C. et Rodriguez, M. (2008). Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. *Movement Disorders, 23*(S3), S548-S559. doi: 10.1002/mds.22062

Osman, A., Kopper, B. A., Barrios, F. X., Osman, J. R. et Wade, T. (1997). The Beck Anxiety Inventory: reexamination of factor structure and psychometric properties. *J Clin Psychol, 53*(1), 7-14.

Paillard, T., Rolland, Y. et de Souto Barreto, P. (2015). Protective Effects of Physical Exercise in Alzheimer's Disease and Parkinson's Disease: A Narrative Review. *J Clin Neurol, 11*(3), 212-219.

Pedersen, B. K. et Saltin, B. (2015). Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scandinavian Journal of Medicine & Science in Sports, 25*, 1-72. doi: 10.1111/sms.12581

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., . . . Small, S. A. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences, 104*(13), 5638-5643. doi: 10.1073/pnas.0611721104

Peters, J., Dauvermann, M., Mette, C., Platen, P., Franke, J., Hinrichs, T. et Daum, I. (2009). Voxel-based morphometry reveals an association between aerobic capacity and grey matter density in the right anterior insula. *Neuroscience, 163*(4), 1102-1108.

Petzinger, G. M., Fisher, B. E., Akopian, G., Holschneider, D. P., Wood, R., Walsh, J. P., . . . Jakowec, M. W. (2011). The role of exercise in facilitating basal ganglia function in Parkinson's disease. *Neurodegener Dis Manag, 1*(2), 157-170.

Petzinger, G. M., Fisher, B. E., McEwen, S., Beeler, J. A., Walsh, J. P. et Jakowec, M. W. (2013a). Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *The Lancet Neurology, 12*(7), 716-726. doi: http://dx.doi.org/10.1016/S1474-4422(13)70123-6

Petzinger, G. M., Fisher, B. E., McEwen, S., Beeler, J. A., Walsh, J. P. et Jakowec, M. W. (2013b). Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol, 12*(7), 716-726. doi: 10.1016/S1474-4422(13)70123-6

Petzinger, G. M., Fisher, B. E., Van Leeuwen, J. E., Vukovic, M., Akopian, G., Meshul, C. K., . . . Jakowec, M. W. (2010). Enhancing neuroplasticity in the basal ganglia: the role of exercise in Parkinson's disease. *Mov Disord, 25 Suppl 1*, S141-145. doi: 10.1002/mds.22782

Petzinger, G. M., Holschneider, D. P., Fisher, B. E., McEwen, S., Kintz, N., Halliday, M., . . . Jakowec, M. W. (2015). The Effects of Exercise on Dopamine Neurotransmission in Parkinson's Disease: Targeting Neuroplasticity to Modulate Basal Ganglia Circuitry. *Brain Plast, 1*(1), 29-39.

Petzinger, G. M., Walsh, J. P., Akopian, G., Hogg, E., Abernathy, A., Arevalo, P., . . . Jakowec, M. W. (2007). Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. *J Neurosci, 27*(20), 5291-5300.

Physiology, C. S. f. E. (1996). *Professional Fitness Lifestyle Consultant 2*. Ottawa.

Poewe, W. (2008). Non-motor symptoms in Parkinson's disease. *European Journal of Neurology, 15*, 14-20.

Pothakos, K., Kurz, M. J. et Lau, Y. S. (2009). Restorative effect of endurance exercise on behavioral deficits in the chronic mouse model of Parkinson's disease with severe neurodegeneration. *BMC Neurosci, 10*, 6.

Prakash, R. S., Voss, M. W., Erickson, K. I. et Kramer, A. F. (2015). Physical Activity and Cognitive Vitality. *Annual Review of Psychology, 66*(1), 769-797. doi: doi:10.1146/annurev-psych-010814-015249

Predovan, D., Fraser, S. A., Renaud, M. et Bherer, L. (2012). The effect of three months of aerobic training on stroop performance in older adults. *J Aging Res, 2012*, 269815. doi: 10.1155/2012/269815

Prodoehl, J., Rafferty, M. R., David, F. J., Poon, C., Vaillancourt, D. E., Comella, C. L., . . . Robichaud, J. A. (2015). Two-Year Exercise Program Improves Physical Function in Parkinson's Disease: The PRET-PD Randomized Clinical Trial. *Neurorehabilitation and Neural Repair, 29*(2), 112-122. doi: 10.1177/1545968314539732

Quaney, B. M., Boyd, L. A., McDowd, J. M., Zahner, L. H., He, J., Mayo, M. S. et Macko, R. F. (2009). Aerobic Exercise Improves Cognition and Motor Function Poststroke. *Neurorehabilitation and Neural Repair*.

Rajput, A. H., Voll, A., Rajput, M. L., Robinson, C. A. et Rajput, A. (2009). Course in Parkinson disease subtypes: A 39-year clinicopathologic study. *Neurology, 73*(3), 206-212. doi: 10.1212/WNL.0b013e3181ae7af1

Rana, A. Q., Ahmed, U. S., Chaudry, Z. M. et Vasan, S. (2015). Parkinson's disease: a review of non-motor symptoms. *Expert Review of Neurotherapeutics, 15*(5), 549-562. doi: 10.1586/14737175.2015.1038244

Reed, J. L. et Pipe, A. L. (2016). Practical Approaches to Prescribing Physical Activity and Monitoring Exercise Intensity. *Canadian Journal of Cardiology, 32*(4), 514-522. doi: http://dx.doi.org/10.1016/j.cjca.2015.12.024

Renaud, M., Bherer, L. et Maquestiaux, F. (2010). A high level of physical fitness is associated with more efficient response preparation in older adults. *J Gerontol B Psychol Sci Soc Sci, 65B*(3), 317-322.

Renaud, M., Maquestiaux, F., Joncas, S., Kergoat, M. J. et Bherer, L. (2010). The effect of three months of aerobic training on response preparation in older adults. *Front Aging Neurosci, 2*, 148.

Reynolds, G. O., Otto, M. W., Ellis, T. D. et Cronin-Golomb, A. (2016). The Therapeutic Potential of Exercise to Improve Mood, Cognition, and Sleep in Parkinson's Disease. *Movement Disorders, 31*(1), 23-38. doi: 10.1002/mds.26484

Ridgel, A. L., Kim, C. H., Fickes, E. J., Muller, M. D. et Alberts, J. L. (2011). Changes in executive function after acute bouts of passive cycling in Parkinson's disease. *J Aging Phys Act, 19*(2), 87-98.

Ridgel, A. L., Vitek, J. L. et Alberts, J. L. (2009). Forced, not voluntary, exercise improves motor function in Parkinson's disease patients. *Neurorehabil Neural Repair, 23*(6), 600-608.

Rieckmann, A., Fischer, H. et Backman, L. (2010). Activation in striatum and medial temporal lobe during sequence learning in younger and older adults: relations to performance. *Neuroimage, 50*(3), 1303-1312.
Rizek, P., Kumar, N. et Jog, M. S. (2016). An update on the diagnosis and treatment of Parkinson disease. *Canadian Medical Association Journal*. doi: 10.1503/cmaj.151179
Roeder, L., Costello, J. T., Smith, S. S., Stewart, I. B. et Kerr, G. K. (2015). Effects of Resistance Training on Measures of Muscular Strength in People with Parkinson?s Disease: A Systematic Review and Meta-Analysis. *PLoS ONE, 10*(7), e0132135. doi: 10.1371/journal.pone.0132135
Roig, M., Skriver, K., Lundbye-Jensen, J., Kiens, B. et Nielsen, J. B. (2012). A Single Bout of Exercise Improves Motor Memory. *PLoS ONE, 7*(9), e44594. doi: 10.1371/journal.pone.0044594
Ruitenberg, M. F., Duthoo, W., Santens, P., Notebaert, W. et Abrahamse, E. L. (2015). Sequential movement skill in Parkinson's disease: A state-of-the-art. *Cortex, 65*, 102-112. doi: 10.1016/j.cortex.2015.01.005
Ryan, S. M. et Nolan, Y. M. (2016). Neuroinflammation negatively affects adult hippocampal neurogenesis and cognition: can exercise compensate? *Neuroscience & Biobehavioral Reviews, 61*, 121-131. doi: http://dx.doi.org/10.1016/j.neubiorev.2015.12.004
Sarazin, M., Deweer, B., Merkl, A., Von Poser, N., Pillon, B. et Dubois, B. (2002). Procedural learning and striatofrontal dysfunction in Parkinson's disease. *Mov Disord, 17*(2), 265-273.
Schapira, A. H. V. et Schrag, A. (2011). Parkinson disease: Parkinson disease clinical subtypes and their implications. *Nat Rev Neurol, 7*(5), 247-248.
Schendan, H. E., Tinaz, S., Maher, S. M. et Stern, C. E. (2013). Frontostriatal and mediotemporal lobe contributions to implicit higher-order spatial sequence learning declines in aging and Parkinson's disease. *Behavioral Neuroscience, 127*(2), 204-221. doi: 10.1037/a0032012
Schuit, A. J., Feskens, E. J., Launer, L. J. et Kromhout, D. (2001). Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. *Med Sci Sports Exerc, 33*(5), 772-777.
Sen, S., Kawaguchi, A., Truong, Y., Lewis, M. M. et Huang, X. (2010). Dynamic changes in cerebello-thalamo-cortical motor circuitry during progression of Parkinson's disease. *Neuroscience, 166*(2), 712-719.
Shin, M.-S., Jeong, H.-Y., An, D.-I., Lee, H.-Y. et Sung, Y.-H. (2016). Treadmill exercise facilitates synaptic plasticity on dopaminergic neurons and fibers in the mouse model with Parkinson’s disease. *Neuroscience Letters, 621*, 28-33. doi: http://dx.doi.org/10.1016/j.neulet.2016.04.015
Shu, H.-F., Yang, T., Yu, S.-X., Huang, H.-D., Jiang, L.-L., Gu, J.-W. et Kuang, Y.-Q. (2014). Aerobic Exercise for Parkinson's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS ONE, 9*(7), e100503. doi: 10.1371/journal.pone.0100503
Siegert, R. J., Taylor, K. D., Weatherall, M. et Abernethy, D. A. (2006). Is implicit sequence learning impaired in Parkinson's disease? A meta-analysis. *Neuropsychology, 20*(4), 490-495.
Smeding, H. M. M., Speelman, J. D., Huizenga, H. M., Schuurman, P. R. et Schmand, B. (2011). Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson's Disease. *Journal of Neurology, Neurosurgery & Psychiatry, 82*(7), 754-760.
Smith, A. D. et Zigmond, M. J. (2003). Can the brain be protected through exercise? Lessons from an animal model of parkinsonism. *Exp Neurol, 184*(1), 31-39.
Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., . . . Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med, 72*(3), 239-252. doi: 10.1097/PSY.0b013e3181d14633

Snow, N. J., Mang, C. S., Roig, M., McDonnell, M. N., Campbell, K. L. et Boyd, L. A. (2016). The Effect of an Acute Bout of Moderate-Intensity Aerobic Exercise on Motor Learning of a Continuous Tracking Task. *PLoS ONE, 11*(2), e0150039. doi: 10.1371/journal.pone.0150039

Speelman, A. D., van de Warrenburg, B. P., van Nimwegen, M., Petzinger, G. M., Munneke, M. et Bloem, B. R. (2011a). How might physical activity benefit patients with Parkinson disease? *Nat Rev Neurol, 7*(9), 528-534. doi: 10.1038/nrneurol.2011.107

Speelman, A. D., van de Warrenburg, B. P., van Nimwegen, M., Petzinger, G. M., Munneke, M. et Bloem, B. R. (2011b). How might physical activity benefit patients with Parkinson disease? *Nat Rev Neurol, 7*(9), 528-534.

Spirduso, W., Francis, K. et MacRae, P. (2005). *Physical Dimensions of Aging*. Human Kinetics, Ill, USA.

Spreen, O. S., Esther; Elisabeth M. S. Sherman (2006). *A compendium of neuropsychological tests: administration, norms, and commentary*.

Stadler, P. F. M. (1998). *Handbook of implicit learning*. CA: Sage Publications.

Stefanova, E. D., Kostic, V. S., Ziropadja, L., Markovic, M. et Ocic, G. G. (2000). Visuomotor skill learning on serial reaction time task in patients with early Parkinson's disease. *Mov Disord, 15*(6), 1095-1103.

Stoessl, A. (2011). Neuroimaging in Parkinson's Disease. *Neurotherapeutics, 8*(1), 72-81.

Stoodley, C. J. et Schmahmann, J. D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex, 46*(7), 831-844. doi: http://dx.doi.org/10.1016/j.cortex.2009.11.008

Svensson, M., Lexell, J. et Deierborg, T. (2015). Effects of Physical Exercise on Neuroinflammation, Neuroplasticity, Neurodegeneration, and Behavior: What We Can Learn From Animal Models in Clinical Settings. *Neurorehabilitation and Neural Repair, 29*(6), 577-589. doi: 10.1177/1545968314562108

Szabo, A. N., McAuley, E., Erickson, K. I., Voss, M., Prakash, R. S., Mailey, E. L., . . . Kramer, A. F. (2011). Cardiorespiratory fitness, hippocampal volume, and frequency of forgetting in older adults. *Neuropsychology, 25*(5), 545-553. doi: 10.1037/a0022733

Tanaka, K., Quadros, A. C., Jr., Santos, R. F., Stella, F., Gobbi, L. T. et Gobbi, S. (2009). Benefits of physical exercise on executive functions in older people with Parkinson's disease. *Brain Cogn, 69*(2), 435-441. doi: 10.1016/j.bandc.2008.09.008

Thenganatt, M. et Jankovic, J. (2014). PArkinson disease subtypes. *JAMA Neurology, 71*(4), 499-504. doi: 10.1001/jamaneurol.2013.6233

Toth, C., Rajput, M. et Rajput, A. H. (2004). Anomalies of asymmetry of clinical signs in parkinsonism. *Mov Disord, 19*(2), 151-157.

Tremblay, M. S. T. S., Warburton, D. E. R. W. E., Janssen, I., Paterson, D. H. P. H., Latimer, A. E. L. E., Rhodes, R. E. R. E., . . . Duggan, M. (2011). New Canadian Physical Activity Guidelines. *Applied Physiology, Nutrition, and Metabolism, 36*(1), 36-46. doi: doi:10.1139/H11-009

Troster, A. I. (2011). Parkinson disease: Deep brain stimulation and neuropsychology: a step forward? *Nat Rev Neurol, advance online publication*.

Uc, E. Y., Doerschug, K. C., Magnotta, V., Dawson, J. D., Thomsen, T. R., Kline, J. N., . . . Darling, W. G. (2014). Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting. *Neurology, 83*(5), 413-425. doi: 10.1212/WNL.0000000000000644

Uhrbrand, A., Stenager, E., Pedersen, M. S. et Dalgas, U. (2015). Parkinson's disease and intensive exercise therapy – a systematic review and meta-analysis of randomized controlled trials. *Journal of the Neurological Sciences, 353*(1–2), 9-19. doi: http://dx.doi.org/10.1016/j.jns.2015.04.004

Vahdat, S., Lungu, O., Cohen-Adad, J., Marchand-Pauvert, V., Benali, H. et Doyon, J. (2015). Simultaneous Brain–Cervical Cord fMRI Reveals Intrinsic Spinal Cord Plasticity during Motor Sequence Learning. *PLoS Biology, 13*(6), e1002186. doi: 10.1371/journal.pbio.1002186

van Eijkeren, F. J. M., Reijmers, R. S. J., Kleinveld, M. J., Minten, A., Bruggen, J. P. t. et Bloem, B. R. (2008). Nordic walking improves mobility in Parkinson's disease. *Movement Disorders, 23*(15), 2239-2243.

van Gelder, B. M., Tijhuis, M. A., Kalmijn, S., Giampaoli, S., Nissinen, A. et Kromhout, D. (2004). Physical activity in relation to cognitive decline in elderly men: the FINE Study. *Neurology, 63*(12), 2316-2321.

van Nimwegen, M., Speelman, A., Hofman-van Rossum, E., Overeem, S., Deeg, D., Borm, G., . . . Munneke, M. (2011). Physical inactivity in Parkinson's disease. *Journal of Neurology*, 1-8.

van Rooden, S. M., Colas, F., Martínez-Martín, P., Visser, M., Verbaan, D., Marinus, J., . . . van Hilten, J. J. (2011). Clinical subtypes of Parkinson's disease. *Movement Disorders, 26*(1), 51-58. doi: 10.1002/mds.23346

van Uem, J. M. T., Marinus, J., Canning, C., van Lummel, R., Dodel, R., Liepelt-Scarfone, I., . . . Maetzler, W. (2016). Health-Related Quality of Life in patients with Parkinson's disease—A systematic review based on the ICF model. *Neuroscience & Biobehavioral Reviews, 61*, 26-34. doi: http://dx.doi.org/10.1016/j.neubiorev.2015.11.014

Verreyt, N., Nys, G. M., Santens, P. et Vingerhoets, G. (2011). Cognitive differences between patients with left-sided and right-sided Parkinson's disease. A review. *Neuropsychol Rev, 21*(4), 405-424.

Verstynen, T. D., Lynch, B., Miller, D. L., Voss, M. W., Prakash, R. S., Chaddock, L., . . . Erickson, K. I. (2012). Caudate Nucleus Volume Mediates the Link between Cardiorespiratory Fitness and Cognitive Flexibility in Older Adults. *J Aging Res, 2012*, 939285. doi: 10.1155/2012/939285

Voelcker-Rehage, C., Godde, B. et Staudinger, U. M. (2010). Physical and motor fitness are both related to cognition in old age. *Eur J Neurosci, 31*(1), 167-176.

Voelcker-Rehage, C., Godde, B. et Staudinger, U. M. (2011). Cardiovascular and coordination training differentially improve cognitive performance and neural processing in older adults. *Front Hum Neurosci, 5*, 26.

Vogel, T., Brechat, P. H., Lepretre, P. M., Kaltenbach, G., Berthel, M. et Lonsdorfer, J. (2009). Health benefits of physical activity in older patients: a review. *Int J Clin Pract, 63*(2), 303-320.

Vogt Weisenhorn, D. M., Giesert, F. et Wurst, W. (2016). Diversity matters – heterogeneity of dopaminergic neurons in the ventral mesencephalon and its relation to Parkinson's Disease. *Journal of Neurochemistry*, n/a-n/a. doi: 10.1111/jnc.13670

Volkers, K. et Scherder, E. (2011). The effect of regular walks on various health aspects in older people with dementia: protocol of a randomized-controlled trial. *BMC Geriatrics, 11*(1), 38.

Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Malkowski, E., Alves, H., . . . Kramer, A. F. (2010). Functional connectivity: A source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia, 48*(5), 1394-1406.

Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T. et Kramer, A. F. (2011). Exercise, brain, and cognition across the life span. *J Appl Physiol, 111*(5), 1505-1513.

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., . . . Kramer, A. F. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci, 2*.

Voss, M. W., Vivar, C., Kramer, A. F. et van Praag, H. Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences, 17*(10), 525-544. doi: 10.1016/j.tics.2013.08.001

Voss, M. W., Vivar, C., Kramer, A. F. et van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences, 17*(10), 525-544. doi: http://dx.doi.org/10.1016/j.tics.2013.08.001

Vucckovic, M. G., Li, Q., Fisher, B., Nacca, A., Leahy, R. M., Walsh, J. P., . . . Petzinger, G. M. (2010). Exercise elevates dopamine D2 receptor in a mouse model of Parkinson's disease: In vivo imaging with [(18)F]fallypride. *Mov Disord*.

Wang, Z., Guo, Y., Myers, K. G., Heintz, R. et Holschneider, D. P. (2015a). Recruitment of the prefrontal cortex and cerebellum in Parkinsonian rats following skilled aerobic exercise. *Neurobiology of Disease, 77*, 71-87. doi: http://dx.doi.org/10.1016/j.nbd.2015.02.020

Wang, Z., Guo, Y., Myers, K. G., Heintz, R. et Holschneider, D. P. (2015b). Recruitment of the prefrontal cortex and cerebellum in Parkinsonian rats following skilled aerobic exercise. *Neurobiology of Disease, 77*(0), 71-87. doi: http://dx.doi.org/10.1016/j.nbd.2015.02.020

Wang, Z., Guo, Y., Myers, K. G., Heintz, R., Peng, Y.-H., Maarek, J.-M. I. et Holschneider, D. P. (2015). Exercise alters resting-state functional connectivity of motor circuits in parkinsonian rats. *Neurobiology of Aging, 36*(1), 536-544. doi: http://dx.doi.org/10.1016/j.neurobiolaging.2014.08.016

Warburton, D. E. R. et Bredin, S. S. D. (2016). Reflections on Physical Activity and Health: What Should We Recommend? *Canadian Journal of Cardiology, 32*(4), 495-504. doi: http://dx.doi.org/10.1016/j.cjca.2016.01.024

Watson, G. S. et Leverenz, J. B. (2010). Profile of Cognitive Impairment in Parkinson's Disease. *Brain Pathology, 20*(3), 640-645.

Weintraub, D., Simuni, T., Caspell-Garcia, C., Coffey, C., Lasch, S., Siderowf, A., . . . Parkinson's Progression Markers, I. (2015). Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. *Mov Disord, 30*(7), 919-927. doi: 10.1002/mds.26170

Werheid, K., Zysset, S., Muller, A., Reuter, M. et von Cramon, D. Y. (2003). Rule learning in a serial reaction time task: an fMRI study on patients with early Parkinson's disease. *Brain Res Cogn Brain Res, 16*(2), 273-284.

Werheid, K., Zysset, S., Müller, A., Reuter, M. et von Cramon, D. Y. (2003). Rule learning in a serial reaction time task: An fMRI study on patients with early Parkinson's disease. *Cognitive Brain Research, 16*(2), 273-284. doi: 10.1016/s0926-6410(02)00283-5

Wong-Yu, I. S. K. et Mak, M. K. Y. (2015). Multi-dimensional balance training programme improves balance and gait performance in people with Parkinson's disease: A pragmatic randomized controlled trial with 12-month follow-up. *Parkinsonism & Related Disorders, 21*(6), 615-621. doi: http://dx.doi.org/10.1016/j.parkreldis.2015.03.022

Wooten, G. F., Currie, L. J., Bovbjerg, V. E., Lee, J. K. et Patrie, J. (2004). Are men at greater risk for Parkinson's disease than women? *Journal of Neurology, Neurosurgery & Psychiatry, 75*(4), 637-639. doi: 10.1136/jnnp.2003.020982

Wu, T. et Hallett, M. (2013). The cerebellum in Parkinson's disease. *Brain, 136*(3), 696-709. doi: 10.1093/brain/aws360

Xu, Q., Park, Y., Huang, X., Hollenbeck, A., Blair, A., Schatzkin, A. et Chen, H. (2010). Physical activities and future risk of Parkinson disease. *Neurology, 75*.

Xu, Y., Yang, J. et Shang, H. (2016). Meta-analysis of risk factors for Parkinson's disease dementia. *Translational Neurodegeneration, 5*, 11. doi: 10.1186/s40035-016-0058-0

Yarnall, A. J., Rochester, L. et Burn, D. J. (2013). Mild cognitive impairment in Parkinson's disease. *Age and Ageing, 42*(5), 567-576. doi: 10.1093/ageing/aft085

Yoon, M. C., Shin, M. S., Kim, T. S., Kim, B. K., Ko, I. G., Sung, Y. H., . . . Kim, C. J. (2007). Treadmill exercise suppresses nigrostriatal dopaminergic neuronal loss in 6-hydroxydopamine-induced Parkinson's rats. *Neurosci Lett, 423*(1), 12-17.

Yu, H., Sternad, D., Corcos, D. M. et Vaillancourt, D. E. (2007). Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage, 35*(1), 222-233. doi: S1053-8119(06)01175-X [pii] 10.1016/j.neuroimage.2006.11.047

Zhang, D., Liu, X., Chen, J. et Liu, B. (2014). Distinguishing Patients with Parkinson's Disease Subtypes from Normal Controls Based on Functional Network Regional Efficiencies. *PLoS ONE, 9*(12), e115131. doi: 10.1371/journal.pone.0115131

Zhang, J., Wei, L., Hu, X., Xie, B., Zhang, Y., Wu, G.-R. et Wang, J. (2015). Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of intrinsic brain activity. *Parkinsonism & Related Disorders, 21*(1), 23-30. doi: http://dx.doi.org/10.1016/j.parkreldis.2014.10.017

Zigmond, M. J. et Smeyne, R. J. (2014). Exercise: Is it a neuroprotective and if so, how does it work? *Parkinsonism & Related Disorders, 20, Supplement 1*, S123-S127. doi: http://dx.doi.org/10.1016/S1353-8020(13)70030-0